NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using bempedoic acid in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: November 2020

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using bempedoic acid with ezetimibe in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 11th January 2021

Second appraisal committee meeting: To be confirmed

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 Bempedoic acid is not recommended, within its marketing authorisations, for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in adults.

1.2 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.

Why the committee made these recommendations

Current treatment for primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia includes statins for lowering low-density lipoprotein cholesterol (LDL-C) levels. Ezetimibe and either alirocumab or evolocumab may be added when patients' LDL-C levels are not lowered enough with the maximally tolerated dose of statins. If it had been recommended, bempedoic acid with ezetimibe would be used when satins are contraindicated or not tolerated, and when ezetimibe alone does not control LDL-C well enough.

Clinical trial evidence suggests that bempedoic acid with ezetimibe may help people lower their LDL-C levels when other lipid-lowering therapies have not reduced them enough. But, 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 ezetemibe may not be as effective at reducing LDL-C levels as alirocumab or evolocumab.

The cost-effectiveness estimates for bempedoic acid with ezetimibe are not what NICE normally considers an acceptable use of NHS resources. So, it cannot be recommended.

2 Information about bempedoic acid

Marketing authorisation indication

Bempedoic acid

2.1 Bempedoic acid (Nilemdo, Daiichi Sankyo) 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'.

Bempedoic acid–ezetimibe

2.2 Bempedoic acid–ezetimibe (Nustendi, Daiichi Sankyo) 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 or
- 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'.

Dosage in the marketing authorisation

2.3 The dosage schedule for bempedoic acid is available in the summary of product characteristics.

2.4 The dosage schedule for bempedoic acid–ezetimibe is available in the summary of product characteristics

Price

2.5 Bempedoic acid and bempedoic acid–ezetimibe costs £55.44 per 28-pack, excluding VAT.

3 Committee discussion

The appraisal committee considered evidence submitted by Daiichi Sankyo, a review of this submission by the evidence review group (ERG), the technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The committee were aware that several issues were resolved during the technical engagement stage, and agreed that:

- it is acceptable that in the model, mixed cohorts are separated into either a primary prevention without heterozygous familial hypercholesterolaemia, or secondary prevention without heterozygous familial hypercholesterolaemia (part of issue 5, see technical report page 27)
- it is acceptable that in the model, the secondary prevention cohort enter at year 3 plus post-cardiovascular event state (part of issue 5, see technical report page 28)
- the ERG's corrections for estimating utility values for all modelled populations were acceptable (issue 8, see technical report page 35)
- the ERG's corrections for the costing of alirocumab and evolocumab administration and the costing of health-states in model were acceptable (issue 9, see technical report page 39).

The committee recognised that there were still areas of uncertainty associated with the analyses presented (see technical report, table 5, page 55), and took these into account in its decision making. The committee discussed the issues (issues 1, 2, 3, 4, 5, 5a, 6, and 7) which were outstanding after the technical engagement stage.

Clinical pathway

People with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia will welcome a new treatment option

3.1 People with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia would welcome a new treatment option. The clinical expert explained that the main aim of treatment is to lower low-density lipoprotein cholesterol (LDL-C) with a statin. People may also have ezetimibe if the maximum dose of statin is not lowering LDL-C enough. If LDL-C levels stay higher than normal and the person has cardiovascular disease or primary heterozygous familial hypercholesterolaemia, evolocumab or alirocumab are offered. The clinical expert explained that some people experience intolerance to statins. Statin intolerance can be difficult to define in clinical practice however some people experience muscle pains and in rare cases muscle breakdown. The patient expert explained the difficulty in appropriately identifying and offering treatment to people with increased levels of LDL-C because often they have no symptoms. In some people with increased LDL-C but who have not had a cardiovascular event (primary prevention), there can be reluctance to continue treatment with a statin. In people who have had a cardiovascular event (secondary prevention) treatment adherence is usually improved. The patient and clinical expert noted that uptake of alirocumab and evolocumab in clinical practice is between 65% and 72% lower than expected. The clinical expert suggested this was because people who are eligible are not navigated through the lipid management pathway appropriately. The patient and clinical expert noted that bempedoic acid is an inexpensive, oral preparation that is easy to use and suitable for people who cannot tolerate statins. The committee concluded that a new treatment option for managing cholesterol would be welcomed.

The company's proposed position of bempedoic acid with ezetimibe in the treatment pathway reflects NHS clinical practice

3.2 At the first committee meeting, the company had positioned bempedoic acid with ezetimibe for people when:

- statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-C well enough and
  - alirocumab or evolocumab are not appropriate (population 2a)
  - alirocumab or evolocumab are appropriate (population 2b).
- the maximally tolerated statin dose with ezetimibe alone does not control LDL-C well enough and
  - alirocumab or evolocumab are not appropriate (population 4a)
  - alirocumab or evolocumab are appropriate (population 4b).

The company's proposed position is narrower than the marketing authorisation (which allows bempedoic acid alone or in combination with a statin without ezetimibe), because they did not anticipate bempedoic acid would be used before ezetimibe in the treatment pathway in the NHS. At the second committee meeting, the company stated that it was no longer seeking a recommendation in population 4a, because the incremental cost-effectiveness ratio (ICER) estimate was too high to be recommended for routine use in the NHS.

The clinical and patient experts agreed with the position of bempedoic acid proposed by the company and noted it would likely not be used before ezetimibe in NHS clinical practice. The committee concluded that the company's proposed position of bempedoic acid in the treatment pathway reflects NHS clinical practice.

Previous treatment with ezetimibe

The network meta-analyses should include only trials in which all patients were having ezetimibe at baseline

3.3 The company's pivotal trial evidence for the effectiveness of bempedoic acid included 7 randomised controlled trials comprising 4 trials of bempedoic acid alone, 1 of bempedoic acid with ezetimibe, 1 of bempedoic acid alone or bempedoic acid with ezetimibe, and 1 trial of bempedoic acid–ezetimibe or bempedoic acid alone. Except for CLEAR Tranquility, the bempedoic acid trials included patients who had not previously had treatment with ezetimibe at baseline or who have had a washout period of lipid-lowering therapies. The ERG noted that this is not reflective of clinical practice because patients would be expected to have previously had ezetimibe according to the treatment pathway (see section 3.2). The clinical expert explained that generalising the clinical effectiveness of previous ezetimibe on improving cardiovascular outcomes and lipid levels depends on the length of time that a patient was having ezetimibe and the time since stopping. The clinical expert noted that the length of time that a patient was having ezetimibe will have an effect on cardiovascular outcomes for patients, and the time from stopping will affect the patients lipid profile. Furthermore, a washout period before bempedoic acid therapy may mitigate the effect of previous ezetimibe treatment. At the second committee meeting, the company updated its analysis to include a restricted network of trials for populations 2a and 2b and 4b, in which all patients were having ezetimibe at baseline (see section 3.8). The updated analysis included all the appropriate data from the CLEAR trials. The company noted that it was not feasible to include a network in which all trials had high background ezetimibe use (80% or more) in population 4b (people having the maximally tolerated statin dose with ezetimibe alone) because all trials reported less than 20% of patients on ezetimibe at baseline (or data were not reported). However, if the threshold were relaxed to 60%, 1 trial could be added to populations 2a and 2b (people who were intolerant to statins) network. The committee

concluded that, given the proposed positioning of bempedoic acid in the treatment pathway, the network meta-analyses should be restricted to include only patients having ezetimibe at baseline.

Baseline LDL-C levels in subpopulations not eligible for alirocumab or evolocumab

Because of the trial limitations, cost-effectiveness results do not reflect the intended positioning of bempedoic acid

3.4 The company used different mean baseline LDL-C levels in its economic model depending on the position of bempedoic acid in the treatment pathway. In patients who could have alirocumab and evolocumab, the company used mean baseline LDL-C levels from patients having alirocumab and evolocumab treatment in the CLEAR trials. However, in patients who could not have alirocumab and evolocumab, baseline LDL-C levels were taken from all patients in the CLEAR trials and did not distinguish between those who could have alirocumab or evolocumab and those who could not. NICE's technology appraisal guidance on alirocumab and evolocumab recommend treatment for:

- primary prevention patients with heterozygous familial hypercholesterolaemia only if LDL-C levels persistently above 5 mmol/L
- secondary prevention patients only if high risk for cardiovascular disease and LDL-C persistently above 4 mmol/L
- secondary prevention patients only if very high risk for cardiovascular disease and LDL-C persistently above >3.5 mmol/L.

The ERG preferred to use LDL-C levels separated by alirocumab or evolocumab eligibility because the baseline LDL-C levels in people not eligible were lower than the levels for those who were eligible. The clinical expert agreed that the baseline LDL-C levels will differ across the subpopulations. The committee agreed with the ERG, and wanted to see results based on the appropriate mean baseline LDL-C levels for the

appropriate subpopulations. After the first committee meeting, NICE requested that the company provide results where baseline LDL-C levels reflect the intended positioning for bempedoic acid (that is, from patients who had already had ezetimibe and according to alirocumab or evolocumab eligibility). In response, the company provided an updated analysis which removed 4 trials from the network for population 4b, and 2 trials from the network for populations 2a and 2b to improve similarity and comparability of baseline LDL-C, but made no adjustment for baseline LDL-C in patients who could not have alirocumab or evolocumab. The company did provide mean baseline LDL-C levels for patients in the CLEAR trials with and without ezetimibe at baseline, however no statistical tests for differences between patients who had previously had ezetemibe and all patients (that is, patients who had and did not have previous ezetimibe) were done. The company also noted that across the bempedoic acid trials, the percentage reduction in LDL-C at 12 weeks was similar for all patients regardless of whether they could have alirocumab or evolocumab or not. The ERG modelled the baseline LDL-C levels to reflect the intended positioning for bempedoic acid (that is, patients who had already had ezetimibe and according to alirocumab and evolocumab eligibility). However, it noted that because of small patient numbers having already had ezetimibe and limited data to determine eligibility for alirocumab or evolocumab, these results are not reliable for decision making. The committee was concerned that the results did not appropriately reflect the intended positioning of bempedoic acid given the limitations of the CLEAR trial informing baseline LDL-C levels. It concluded that because of the trial limitations, cost-effectiveness results do not reflect the intended positioning of bempedoic acid in the treatment pathway.

Subgroup analyses

Because of trial limitations, subgroup analyses could not be provided by heterozygous familial hypercholesterolaemia and cardiovascular risk status

3.5 The final NICE scope specified that subgroup analysis by cardiovascular risk and presence of heterozygous familial hypercholesterolaemia should be considered for the subgroups who were eligible for alirocumab or evolocumab. NICE's technology appraisals guidance for evolocumab and alirocumab made recommendations for these different subgroups (see section 3.4). The company noted that the proportion of patients with heterozygous familial hypercholesterolaemia in its trials were small. It noted that CLEAR Wisdom included the largest group of patients with heterozygous familial hypercholesterolaemia, and subgroup analysis suggested that the treatment effect is consistent with the non-heterozygous familial hypercholesterolaemia population. At technical engagement, the company presented cost-effectiveness results in 7 subgroups according to cardiovascular risk and heterozygous familial hypercholesterolaemia. The same treatment effect for bempedoic acid was used in each subgroup based on the assumption that the treatment effect would be similar in patients with and without heterozygous familial hypercholesterolaemia and with and without previous cardiovascular disease. The clinical expert explained that a common treatment effect should not be assumed across subgroups of heterozygous familial hypercholesterolaemia, non-familial hypercholesterolaemia and mixed dyslipidaemia because they each have distinct lipid profiles. The ERG considers that the company's subgroup analyses show the cost effectiveness of bempedoic acid is correlated with the baseline LDL-C level rather than with alirocumab or evolocumab eligibility. Further, the ERG noted that the company's trials had not been designed to detect statistical differences across cardiovascular risk and heterozygous familial hypercholesterolaemia. Also the subgroup analysis had low patient numbers and was underpowered. The company did not update their subgroup analyses for heterozygous familial hypercholesterolaemia and

cardiovascular risk status using their latest network meta-analysis (see section 3.8). The committee acknowledges that because the data needed were not sufficiently collected in the CLEAR trials, it is not possible to do the appropriate subgroup analyses for heterozygous familial hypercholesterolaemia and cardiovascular risk status. The committee concluded that the company's subgroup analysis for these subgroups were not sufficient, because a treatment effect was assumed to be the same across patients with and without heterozygous familial hypercholesterolaemia, and with and without previous cardiovascular disease.

Analyses by primary and secondary prevention population

Because of trial limitations, analyses based on efficacy data directly related to the primary and secondary prevention populations could not be done

3.6 At technical engagement, the ERG noted that efficacy data for bempedoic acid are limited in primary prevention and patients with heterozygous familial hypercholesterolaemia. The clinical expert noted that it is possible to assume a similar treatment effect of bempedoic acid on lipid reduction across primary and secondary prevention status. However, it is not reasonable to assume a similar treatment effect on cardiovascular prevention, because cardiovascular risk is higher in secondary prevention patients. To avoid modelling a mixed prevention cohort, the company accepted the ERG's suggestion to model the subpopulations according to most of the population in the CLEAR trials. The populations were modelled as follows:

- subpopulation 2a, primary prevention without heterozygous familial hypercholesterolaemia;
- subpopulation 2b, secondary prevention without heterozygous familial hypercholesterolaemia;
- subpopulation 4a, secondary prevention without heterozygous familial hypercholesterolaemia;

- subpopulation 4b, secondary prevention without heterozygous familial hypercholesterolaemia.

However, the ERG noted that not all patients in the trials included in the company's original network meta-analysis supporting the data for subpopulations 2b and 4b come from trial populations without heterozygous familial hypercholesterolaemia in secondary prevention. Additionally, not all patients in the network meta-analysis supporting the data for subpopulation 2a come from trial populations without heterozygous familial hypercholesterolaemia in primary prevention. At the second appraisal meeting, NICE requested analyses based on efficacy data directly relevant to the intended subpopulation should be done to provide reliable cost-effectiveness estimates. The company noted that limiting to primary prevention and secondary prevention trials to inform relevant positions is challenging, because trials had mixed populations, and reporting of cardiovascular risk and previous cardiovascular events was unclear. As such, the company did not present updated results in response to this request. The committee concluded that the clinical heterogeneity resulting from generalised subgroup efficacy data is unlikely to be resolved because of the limitations in the data from the CLEAR trials.

Primary cardiovascular risk and cardiovascular event risk could not be collected from the company's CLEAR trials data

3.7 The company's model calculated background cardiovascular risks by converting the SCORE risk algorithm in European Society of Cardiology guidelines for a high-risk population into a QRISK3 risk. The subsequent annual risk was then used to estimate annual risk for the different cardiovascular events based on the relative rates of first events in Ward et al., 2007. The company noted that this approach is consistent with the approach in NICE's clinical guideline on cardiovascular disease: risk assessment and reduction, including lipid modification. The ERG considered that primary cardiovascular risks and cardiovascular event

history in the CLEAR trials may be more appropriate to use than other sources. The ERG considered that the true risk for primary cardiovascular events would lie somewhere between the company's base-case analysis (a 10-year risk of around 30% for myocardial infarction, ischemic stroke or cardiovascular death estimated using the SCORE risk) and the company's scenario analysis provided during the clarification stage (a 10-year risk of 20% for myocardial infarction, ischemic stroke or cardiovascular death). After the first committee meeting, NICE requested that the analyses use data from the CLEAR trials to inform baseline cardiovascular risk and event history in the model. The company reiterated that the parameters needed to reliably calculate cardiovascular risks using the QRISK3 algorithm have not been captured in the CLEAR trial datasets and cannot be obtained from published data. Additionally, the company noted that they were unable to use previous cardiovascular events from the CLEAR trials to estimate what previous events would have happened in the model, because these data were also not available from the CLEAR trials. The ERG reported, that in absence of the CLEAR trial data, using Ward et al., 2007 to inform the distribution of previous cardiovascular events to be a reasonable alternative. The ERG presented the updated scenario analysis from the first appraisal meeting using the ERG preferred network meta-analysis (see section 3.8) for population 2a (that is, patients who were statin intolerant and not eligible for alirocumab or evolocumab). The ERG reported that the same change in risk (from the company's base-case analysis of a 10-year risk of around 30%, to the scenario analysis of a 10-year risk of 20%) resulted in an increase in the ICER of about £7,500 per quality adjusted life year gained (QALY). The committee understood that data on primary cardiovascular risks and cardiovascular event history could not be obtained from the CLEAR trials. They concluded that using data from Ward et al., 2007 was a reasonable alternative, and the resulting uncertainty in the cost-effectiveness results could not be resolved.

Methodological uncertainty

The ERG's updated network meta-analysis is the most suitable for decision making

3.8 The ERG noted that the company's network meta-analysis submitted at technical engagement had high levels of statistical and clinical heterogeneity present. This included differences between trials in terms of baseline cardiovascular risk, statin intensity, proportion of patients having lipid-lowering therapy for primary prevention, and proportions of patients with heterozygous familial hypercholesterolaemia. It also noted that the high residual deviance implied that the company's network meta-analysis would poorly predict the data from the trials used in the analysis. At the first appraisal meeting, the committee considered the high levels of statistical and clinical heterogeneity present in the company network meta-analysis to be unreliable for decision making. The committee noted that neither the ERG's or company's network meta-analysis were suitable, and preferred to see network meta-analyses for both the statin intolerant (population 2) and maximally tolerated statin populations (population 4), with improved statistical fit, reduced clinical heterogeneity. After the first appraisal committee meeting, NICE requested that the company do an analysis which builds upon the network meta-analyses done by the ERG and presented in the first appraisal meeting to reduce statistical and clinical heterogeneity. As part of the analysis, NICE also asked the company to identify any additional trials that meet the following:

- People in the trial have had treatment with ezetimibe before randomisation (see section 3.3).
- People in the trials have similar unadjusted baseline LDL-C levels (see section 3.4).
- Use appropriate trials to inform treatment efficacy for primary prevention (population 2a) and secondary prevention (population 2b and 4b) (see sections 3.6 and 3.7).

- Trials that have other similar baseline characteristics such as cardiovascular disease risk, heterozygous familial hypercholesterolaemia, type of statin, sex, and ethnicity (see section 3.5).

In response, the company presented 2 further network meta-analyses:

- The company presented an additional network meta-analysis, which included several changes in line with the requests by NICE (see sections 3.3, 3.4, 3.5, 3.6 and 3.7). The committee agreed with the ERG and remained concerned that there was substantial unresolved clinical heterogeneity between the trials included in the company's additional network meta-analysis, and the results were not suitable for decision making.

- The company updated the ERG preferred network meta-analysis to include all available data for bempedoic acid in patients having ezetimibe at baseline from the CLEAR trials that the ERG did not previously have access to. The ERG considered that the updated ERG analysis met the requests from NICE.

The committee concluded that the company's updated ERG network meta-analysis was preferred and the most suitable for decision making.

Long-term treatment effect of bempedoic acid

The latest available data should be used to inform long-term treatment effect

3.9 The primary efficacy outcome of all relevant bempedoic acid trials was percentage change from baseline LDL-C at 12 weeks. The company model assumed that results achieved at 12 weeks were maintained for the duration of the model's time horizon, or until treatment is stopped. In the first appraisal meeting, the company stated that improvements in LDL-C continued through 52 and 78 weeks but did not include this data in their updated analyses for the second appraisal meeting. The ERG noted that

there may be a slight waning of treatment effect with bempedoic acid beyond 12 weeks in the data for CLEAR Tranquility and CLEAR Serenity. The company acknowledged that there are differences seen in the CLEAR trials but considered these to be related to treatment stopping rather than a waning treatment effect. Clinical experts could not comment on the potential waning effect of bempedoic acid. The committee concluded that it would like to see the latest available data informing the long-term treatment effect of bempedoic acid.

Evidence of the effect of bempedoic acid on cardiovascular outcomes should be provided

3.10 The company noted that it modelled the relationship between LDL-C reduction and cardiovascular risk based on the Cholesterol Treatment Trialist Collaboration meta-analyses of statin studies. The company highlighted that although bempedoic acid and statins both inhibit cholesterol synthesis in the liver, bempedoic acid is inactive in skeletal muscle, unlike statins. At the second appraisal meeting, the committee expressed a concern that the link between changes in LDL-C levels and cardiovascular outcomes used in the company model, may not be appropriate for bempedoic acid because the mechanism of action of bempedoic acid is different to that of statins. The committee concluded that it would like to see evidence of the direct impact of bempedoic acid on cardiovascular outcomes.

Cost-effectiveness results

The ERG's updated base case includes the committee's preferences

3.11 The ERG's revised base case (which is the same as the company's updated ERG preferred network meta-analysis) included the committee's preferred network meta-analysis. The ERG network meta-analysis comprised of restricted networks of trials for populations 2a and 2b (people who were intolerant to statins) and population 4b (people having the maximally tolerated statin dose) in which all patients were having

ezetimibe at baseline (see section 3.3), and thus were aligned with the company's proposed positioning of bempedoic acid in the treatment pathway. The results of the ERG's revised base case included the cost of the bempedoic acid–ezetimibe fixed dose combination tablet only. The committee was aware that this was cheaper than separate tablets for bempedoic acid and ezetimibe. The committee concluded that the revised ERG base case was the most suitable for decision making.

Because of the uncertainty, an acceptable ICER is below £20,000 per QALY gained and above £30,000 per QALY lost

3.12 For population 2a, the ICER resulted in additional costs and a gain of QALYs. For population 2b and 4b, the ICER resulted in cost savings and a loss of QALYs. NICE's guide to the methods of technology appraisal notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented.

The committee noted the high level of uncertainty. In particular:

- the committee remained uncertain that the results appropriately reflect the intended positioning of bempedoic acid given the limitations of the CLEAR trial informing baseline LDL-C levels (see section 3.4)
- subgroup analyses by cardiovascular risk and heterozygous familial hypercholesterolaemia could not be appropriately done (see section 3.5)
- the appropriate analyses based on efficacy data directly related to the primary and secondary prevention populations could not be done (see section 3.6)
- that primary cardiovascular risks and cardiovascular event history could not be informed by the CLEAR trial (see section 3.7)

- no evidence were provided on the long-term impact of bempedoic acid on cardiovascular outcomes (see section 3.10)

Therefore, the committee agreed that conservative thresholds for populations 2a, 2b and 4b should be adopted. The committee concluded that an acceptable ICER for population 2a would be below £20,000 per QALY gained, and an acceptable ICER for populations 2b and 4b would be above £30,000 per QALY lost.

For population 2a, the most plausible ICERs are above what is considered a cost-effective use of NHS resources

3.13 Using the committee's preferred assumptions (see section 3.11) the most plausible ICER for population 2a (statins are contraindicated or not tolerated and alirocumab or evolocumab are not eligible) is £23,824 per QALY gained. Therefore, the committee concluded that bempedoic acid with ezetimibe could not be considered a cost-effective use of NHS resources.

For population 2b, the most plausible ICERs are below what is considered a cost-effective use of NHS resources

3.14 Using the committee's preferred assumptions (see section 3.11) the most plausible ICER for population 2b (statins are contraindicated or not tolerated and eligible for alirocumab or evolocumab) resulted in cost savings and a loss of QALYs (less than £30,000 saved per QALY lost). Because of confidential discounts for alirocumab and evolocumab, the exact ICER for population 2b cannot be reported here. Therefore, the committee concluded that bempedoic acid with ezetimibe could not be considered a cost-effective use of NHS resources.

For population 4b, the most plausible ICERs are below what is considered a cost-effective use of NHS resources

3.15 Using the committee's preferred assumptions (see section 3.11) the most plausible ICER for population 4b (maximally tolerated statin dose and eligible for alirocumab or evolocumab) resulted in cost savings and a loss

of QALYs (less than £30,000 saved per QALY lost). Because of confidential discounts for alirocumab and evolocumab the exact ICER for population 4b cannot be reported here. Therefore, the committee concluded that bempedoic acid with ezetimibe could not be considered a cost-effective use of NHS resources.

Other factors

There are no equalities issues

3.16 No equality or social value judgement issues were identified.

There are no additional benefits not already captured in the economic analysis

3.17 The committee understood that there is an unmet need for patients who cannot tolerate statins. The committee was aware that bempedoic acid is an oral preparation compared with alirocumab and evolocumab which are administered subcutaneously and took this into account in its decision making. The committee concluded that there were no additional benefits associated with this treatment that had not been captured in the economic analysis.

Conclusion

Bempedoic acid is not recommended

3.18 The committee concluded that bempedoic acid was not recommend as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in adults. The committee was concerned about the clinical effectiveness of bempedoic acid because of the lack of long-term data on cardiovascular outcomes in the pivotal trials. Further, the committee were concerned that requested subgroup analyses relating to cardiovascular risk and heterozygous familial hypercholesterolaemia status had not been appropriately done. Given the limitations of the CLEAR trials, it was not possible to use efficacy data directly related to the primary and secondary prevention populations. The committee also remained concerned that the

cost-effectiveness estimates did not appropriately reflect the intended positioning of bempedoic acid (for patients who had already had ezetimibe and according to alirocumab or evolocumab eligibility) given the limitations of the trials informing baseline LDL-C levels.

The cost-effectiveness estimates using the committee's preferred assumptions did not represent what is considered a cost-effective use of NHS resources. The committee therefore concluded that bempedoic acid with ezetimibe could not be recommended for routine use in the NHS.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology be considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Stephen O'Brien
Chair, appraisal committee
November 2020

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Cameron Collins
Technical lead

Victoria Kelly
Technical adviser

Gavin Kenny
Project manager

ISBN: [to be added at publication]