NICE National Institute for Health and Care Excellence

NICE guidance

Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia

Technology appraisal guidance
Published: 28 April 2021

www.nice.org.uk/guidance/ta694

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance is the basis of QS100.

1 Recommendations

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.

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. Bempedoic acid with ezetimibe would be used when statins 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 lower 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 ezetimibe may not be as effective at reducing LDL-C levels as alirocumab or evolocumab.

Despite the uncertainty, the cost-effectiveness estimates for bempedoic acid with ezetimibe, when statins are contraindicated or not tolerated, are within what NICE normally considers an acceptable use of NHS resources. So, bempedoic acid with ezetimibe is 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,
- 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.

2.6 The company has a commercial arrangement (commercial access agreement). This makes bempedoic acid and bempedoic acid–ezetimibe available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

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.

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 and responses to the appraisal consultation document 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.

During the appraisal, the company decided that it was no longer seeking a recommendation in the maximally tolerated statin population (populations 4a and 4b), because the incremental cost-effectiveness ratio (ICER) estimates were 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, 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 of patients in the trial had previously had ezetimibe). 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

Scenario analyses for adjusted baseline LDL-C levels were sufficient for decision making

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 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 ERG presented results for adjusted baseline LDL-C levels in population 2a, according to alirocumab and evolocumab eligibility. 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 ezetimibe 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 to alirocumab or evolocumab, these results are not reliable for decision making. The committee understood the added uncertainty around the results given the limitations of the CLEAR trial informing baseline LDL-C levels. It concluded that cost-effectiveness results from scenario analyses were sufficient for decision making.

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 considered 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 acknowledged that because the data needed were not 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 analyses for these subgroups were not sufficient for decision making, 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.

However, the ERG noted that not all patients in the trials included in the company's original network meta-analysis supporting the data for subpopulation 2b come from trial populations without heterozygous familial hypercholesterolaemia in secondary prevention. Also, 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 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 resolvable 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 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 had 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., to inform the distribution of previous cardiovascular events is a reasonable alternative. At the second committee meeting, the ERG presented the updated scenario analysis from the first committee 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 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., 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 with improved statistical fit and 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) (see section 3.6 and section 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:

- An additional network meta-analysis, which included several changes in line with the requests by NICE (see sections 3.3 to 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.
- An update of the ERG preferred network meta-analysis to include all available data for bempedoic acid in patients having ezetimibe at baseline from the CLEAR trials, to which 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. In response to the appraisal consultation document, the company provided updated cost-effectiveness results using the committee's preferred network meta-analysis.

Long-term treatment effect of bempedoic acid

There is uncertainty with the evidence informing the long-term treatment effect of bempedoic acid

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. 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. In response to the appraisal consultation document, the

company highlighted evidence from the CLEAR Harmony open-label extension study which showed a mean LDL-C reduction from baseline in CLEAR Harmony of -14.9% and -14.4% at 12 and 78 weeks. The ERG noted that the data relate to people who have maximally tolerated statin levels, which is a population that the company is no longer seeking recommendation for, and it also includes people who have not previously had ezetimibe. The ERG considered that there may be a slight waning of treatment effect with bempedoic acid beyond 12 weeks but it did not know if a similar waning would be seen with the comparators. Therefore, the ERG explored 2 scenarios to show what effect a treatment waning effect on LDL-C could have on the cost-effectiveness results using data from CLEAR Serenity (study data directly relating to the statin intolerant population). Clinical experts could not comment on the potential waning effect of bempedoic acid. The company and the ERG noted that treatment waning effects could be because of other factors (for example when people stop following advice on diet and exercise improvements) and not just lipid-lowering drug efficacy. The committee concluded that there is uncertainty in the evidence informing the long-term treatment effect of bempedoic acid.

Evidence of the direct effect on cardiovascular outcomes is not available

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 noted that although bempedoic acid and statins both inhibit cholesterol synthesis in the liver, a differentiating factor is that, unlike statins, bempedoic acid is inactive in skeletal muscle. 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. In response to the appraisal consultation document, the company provided additional information reinforcing that the cardiovascular benefits of LDL-C lowering are independent of the methods by which it is achieved. The committee accepted the association between LDL-C lowering and cardiovascular benefits, but concluded that it would have liked to have

seen 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) provided at the second appraisal meeting 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) 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. In response to the appraisal consultation document, the company provided updated cost-effectiveness results based on the committee's preferred modelling assumptions with a commercial arrangement for bempedoic acid and bempedoic acid–ezetimibe.

Because of the uncertainty, an acceptable ICER is below £20,000 per quality-adjusted life year (QALY) gained and above £30,000 per QALY lost

3.12 The committee recalled that the company was no longer seeking a recommendation in the maximally tolerated statin population (population 4a and 4b) (see section 3.2). For population 2a, the ICER resulted in additional costs and a gain of QALYs. For population 2b, 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)
- the committee remain uncertain about the evidence 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 and 2b 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 population 2b would be above £30,000 per QALY lost.

Bempedoic acid with ezetimibe is recommended as 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 not eligible for alirocumab or evolocumab) was less than £20,000 per QALY gained for bempedoic acid and bempedoic acid–ezetimibe. Because of the confidential discount for bempedoic acid and bempedoic acid–ezetimibe, the exact ICER for population 2a cannot be reported here.

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) was more than £30,000 saved per QALY lost for bempedoic acid and bempedoic acid–ezetimibe. Because of the confidential discount for bempedoic acid and bempedoic acid–ezetimibe, the exact ICER for population 2b cannot be reported here.

3.15 The committee concluded that bempedoic acid with ezetimibe (both as separate tablets and in a fixed-dose combination) is cost effective for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in adults for whom statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-C well enough.

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 with ezetimibe is recommended

3.18 The committee concluded that 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 for whom statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-C well enough. 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, and that appropriate subgroup analyses relating to cardiovascular risk and heterozygous familial hypercholesterolaemia could not be provided. However, it noted that further data were unlikely to become available. The cost-effectiveness results based on the committee's preferred modelling assumptions with a commercial arrangement for bempedoic acid and bempedoic acid–ezetimibe represent a cost-effective use of NHS resources. The committee therefore concluded that bempedoic acid with ezetimibe be recommended for routine use in the NHS in people for whom statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-C well enough.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has primary hypercholesterolaemia or mixed dyslipidaemia and the doctor responsible for their care thinks that bempedoic acid with ezetimibe is the right treatment, it should be available for use, in line with NICE's recommendations.

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 and Sally Doss
Technical adviser(s)

Gavin Kenny
Project manager

Update information

Minor changes since publication

September 2021: We added a clarification to 'Why the committee made these recommendations' to say that NICE was not able to evaluate bempedoic acid plus ezetimibe with low intensity statins when higher intensity statins are not tolerated. We also clarified that the cost-effectiveness estimates were for bempedoic acid plus ezetimibe when statins are contraindicated or not tolerated.

ISBN: 978-1-4731-4099-8