Healthcare Improvement Scotland | SMC Advice on new medicines

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SMC2363

bempedoic acid 180mg film-coated tablets (Nilemdo®)

Daiichi Sankyo UK Ltd

4 June 2021

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission

bempedoic acid (Nilemdo®) is accepted for restricted use within NHSScotland.

Indication under review: in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- In combination with a statin, or a statin with other lipid-lowering therapies in patients unable to reach low-density lipoprotein cholesterol (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 contra-indicated.

SMC restriction: for use in combination with ezetimibe in patients who are:

- statin intolerant or for whom a statin is contra-indicated
  and
- where ezetimibe alone does not appropriately control LDL-C
  and
- where proprotein convertase subtilisin/ kexin type 9 (PCSK9) inhibitors are not appropriate

In two phase III studies in patients intolerant to statins, the percentage reduction in LDL-C to 12-weeks was significantly larger with bempedoic acid compared with placebo.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

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 contra-indicated.[1]

Dosing Information

The recommended dose of bempedoic acid is 180mg once daily taken orally with or without food and swallowed whole.[1]

Product availability date

October 2020

Summary of evidence on comparative efficacy

Bempedoic acid is a novel oral lipid-lowering medicine. It is a prodrug that is activated in the liver to ETC-1002-Coenzyme A (ETC-1002-CoA), which subsequently inhibits adenosine triphosphate citrate lyase (ACL), an enzyme upstream of 3-hydroxyl-3-methylglutaryl Coenzyme A (HMG-CoA) reductase in the cholesterol synthesis pathway. Inhibition of cholesterol synthesis triggers the upregulation of low-density lipoprotein (LDL) receptor (LDLR) expression in the liver resulting in increased clearance of LDL particles and lowering of LDL cholesterol (LDL-C) in the blood. Additionally, inhibition of ACL by ETC-1002-CoA results in concomitant suppression of hepatic fatty acid biosynthesis.[1]

The submitting company has requested that SMC considers the use of bempedoic acid when positioned in combination with ezetimibe, in patients who are statin intolerant or for whom a statin is contraindicated, and ezetimibe alone does not appropriately control LDL-C and

- PCSK9 inhibitors are not appropriate (position 1a), or
- PCSK9 inhibitors are appropriate (position 1b)

Two randomised, double-blind phase III studies compared bempedoic acid with placebo in patients with primary hypercholesterolaemia and mixed dyslipidaemia in patients who were statin intolerant (CLEAR Serenity[2] and CLEAR Tranquility[3]). In CLEAR Tranquility, all patients also received ezetimibe. The company submission included two supporting studies in patients also receiving the maximum tolerated dose of a statin (CLEAR Harmony[4] and CLEAR Wisdom[5]) which are not relevant to the company's positioning in this submission.

In CLEAR Serenity and CLEAR Tranquility, eligible patients were aged ≥18 years, requiring additional lipid-lowering therapy for primary or secondary prevention of cardiovascular (CV)

events. At initial screening, they had fasting LDL-C of ≥130mg/dL (3.4mmol/L) for primary prevention and ≥100mg/dL (2.6mmol/L) for patients with heterozygous familial hypercholesterolaemia (HeFH) and / or those for secondary prevention (CLEAR Serenity) or ≥100mg/dL (2.6mmol/L) for patients already taking ezetimibe and ≥120mg/dL (3.1mmol/L) for patients not taking ezetimibe (CLEAR Tranquility). In both studies, patients were required to have a fasting LDL-C of ≥70mg/dL (1.8mmol/L) one week before randomisation. They had a history of statin intolerance due to adverse effects defined in CLEAR Serenity as intolerance to at least two statins, one at low dose, and in CLEAR Tranquility as intolerance to at least one statin at more than low dose. [2, 3, 6]

In both studies, eligible patients were randomised in a ratio of 2:1 to receive bempedoic acid 180mg once daily or matching placebo. In CLEAR Tranquility, all patients received open-label ezetimibe 10mg daily during the 4-week run-in phase and this continued during the study. Study treatment was continued for 24 weeks in CLEAR Serenity and for 12 weeks in CLEAR Tranquility. Randomisation was stratified by presence or absence of HeFH and by primary or secondary prevention (CLEAR Serenity). [2, 3, 6]

The primary efficacy outcome in both studies was the percentage change in LDL-C from baseline to week 12 and this was significantly greater with bempedoic acid compared with placebo in both studies. Details are presented in Table 1. A hierarchical statistical testing strategy was applied to key efficacy outcomes with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Therefore the results reported for these outcomes are descriptive only and not inferential (no p-values reported). The efficacy outcomes were tested in the following order:

1. Percent change from baseline to week 12 in LDL-C
2. Percent change from baseline to week 24 in LDL-C.
3. Percent change from baseline to week 12 in non-HDL-C.
4. Percent change from baseline to week 12 in total cholesterol.

Bempedoic acid resulted in significantly greater percentage reductions for each secondary outcome compared with placebo in both studies as detailed in Table 1.[2, 3, 6]

Table 1. Results for primary and key secondary efficacy outcomes in CLEAR Serenity and CLEAR Tranquility [2, 3, 6]

	CLEAR Serenity		**CLEAR Tranquility**	
	Bempedoic acid (n=234)	**Placebo (n=111)**	**Bempedoic acid (n=181)**	**Placebo (n=88)**
Primary efficacy outcome				
Baseline LDL-C (mg/dL)	158.5	155.6	129.8	123.0
LS Mean % change in LDL-C	-23%	-1.2%	-24%	5.0%

LS mean difference (95% CI)	-21% (-25 to -18) p<0.001		-28% (-34% to -22%) p<0.001	
Secondary efficacy outcomes: LS Mean % change in:				
LDL-C (24wk), %	-21	-2.3	N/A	N/A
LS mean difference (95% CI)	-19 (-23 to -15) p<0.001		-	
Non-HDL-C (12wk), %	-18	-0.1	-18	5.2
LS mean difference (95% CI)	-18 (-21 to -15) p<0.001		-24 (-29 to -18) p<0.001	
TC (12wk), %	-15	-0.6	-15	2.9
LS mean difference (95% CI)	-15 (-17 to -12) p<0.001		-18 (-22 to -14) p<0.001	
LS: least squares, CI: confidence interval, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TC: total cholesterol; wk: week.				

The proposed positioning by the submitting company is for the use of bempedoic acid with ezetimibe, for patients who are statin intolerant or for whom a statin is contraindicated. However, although all patients in the CLEAR Tranquility study received ezetimibe in addition to study medication, in CLEAR Serenity, only a small proportion (14%) of study patients received ezetimibe.

The submitting company performed a Bayesian network meta-analysis (NMA) to compare the efficacy of bempedoic acid plus ezetimibe (data from CLEAR Tranquility[3] and CLEAR Serenity[2] studies), alirocumab plus ezetimibe (data from ODYSSEY CHOICE II[7] study), and ezetimibe alone (data from CLEAR Serenity, CLEAR Tranquility and ODYSSEY CHOICE II studies).[2, 3, 7] The target patient population was defined as adult patients with hyperlipidaemia at moderate or high risk of or with atherosclerotic cardiovascular disease (ACVD) who require further lipid-lowering therapy despite statin treatment at the maximally tolerated dose or who are considered statin intolerant. To reflect the proposed positioning, only studies with patients considered statin intolerant and subgroups of patients receiving ezetimibe at baseline were included in the NMA. The outcome assessed was the difference from baseline to week 12, in percentage change in LDL-C. Results indicated that there was a greater percentage reduction in LDL-C from baseline to week 12 with bempedoic acid plus ezetimibe when compared with ezetimibe alone, and with alirocumab plus ezetimibe when compared with ezetimibe alone, and there was less of a reduction with bempedoic acid plus ezetimibe when compared with alirocumab plus ezetimibe. No results were available for the comparison with evolocumab plus ezetimibe.

Summary of evidence on comparative safety

A pooled safety analysis has been reported for the four phase III CLEAR studies, which included 2,424 patients treated with bempedoic acid and 1,197 patients treated with placebo. The duration of study treatment varied across the four studies from 12 weeks in CLEAR Tranquility to 52 weeks in CLEAR Harmony and Wisdom.[6, 8]

In this pooled safety analysis, a treatment emergent adverse event was reported in 73% each of patients treated with bempedoic acid and placebo and these were serious in 14% and 13% of patients respectively. Treatment related adverse events were reported in 24% of bempedoic acid treated patients and 20% of placebo treated patients. An adverse event led to study treatment discontinuation in 11% and 7.8% of patients respectively. These discontinuations were mainly due to gastrointestinal disorders (1.5% versus 0.7%) or musculoskeletal and connective tissue disorders when used in addition to statins (2.8% versus 1.9%).[6, 8]

In the pooled safety analysis, the most frequently reported treatment-emergent adverse events of any grade and adverse events of special interest in the bempedoic acid and placebo groups were: nasopharyngitis (7.4% and 8.9%), myalgia (4.9% and 5.3%), urinary tract infection (4.5% and 5.5%), arthralgia (4.1% and 4.8%), new onset or worsening diabetes (4.0% and 5.6%), upper respiratory tract infection (3.9% and 3.7%), muscle spasms (3.7% and 2.6%), dizziness (3.4% and 3.4%), diarrhoea (3.4% and 3.3%), back pain (3.1% and 2.3%), pain in extremity (3.1% and 1.8%), headache (2.8% and 3.1%), decreased haemoglobin (2.8% and 1.8%), increased hepatic enzymes (2.8% and 1.3%), anaemia (2.5% and 1.6%), fatigue (2.2% and 3.5%), increased blood uric acid level (2.1% and 0.5%), hyperuricaemia (1.7% and 0.6%) and gout (1.4% and 0.4%).[6, 8]

Summary of clinical effectiveness issues

Statins are the treatment of choice for patients with hypercholesterolaemia. However, a proportion of patients have contra-indications to, or are unable to tolerate statins and therefore require alternative lipid-lowering therapy to reduce LDL-C. For these groups of patients, treatment options are limited to ezetimibe and for a smaller number of higher risk patients the proprotein convertase subtilisin/ kexin type 9 (PCSK9) inhibitors.[6, 9, 10] SMC has accepted restricted use of PCSK9 inhibitors by specialists only and in patients at high cardiovascular risk as follows:

- patients HeFH and LDL-C ≥5.0mmol/L for primary prevention of cardiovascular events or,
- patients with HeFH and LDL-C ≥3.5mmol/L for secondary prevention of cardiovascular events or,
- patients at high risk due to previous cardiovascular events and LDL-C ≥4.0mmol/L or
- patients with recurrent/polyvascular disease and LDL-C ≥3.5mmol/L.

The submitting company has proposed that bempedoic acid is considered for use in combination with ezetimibe, in patients who are statin intolerant or for whom a statin is contraindicated and where ezetimibe alone does not appropriately control LDL-C.

The percentage reduction in LDL-C was statistically significantly larger with bempedoic acid compared with placebo in both key CLEAR studies and this was supported by significantly greater improvements in secondary study outcomes. [2, 3, 6]

The primary efficacy outcome, mean percentage change in LDL-C is accepted as a surrogate endpoint for the reduction of CV events but published CLEAR studies have not assessed the effect of bempedoic acid on CV outcomes. An ongoing CLEAR Outcomes study will assess a composite of CV death, nonfatal myocardial infarction, nonfatal stroke or coronary revascularisation in more than 14,000 patients with a history or high risk of CV disease (CVD), who were statin intolerant and fasting LDL-C of ≥100mg/dL (2.6mmol/L). This study is not expected to report until 2023.[11]

In both studies, the treatment effect was reported as a relative reduction (percentage reduction versus baseline) and not as an absolute reduction and was assessed after 12 weeks, which is considered acceptable by the EMA but is short for chronic treatment of hypercholesterolaemia. The secondary outcome of LDL-C reduction to week 24 has indicated that the treatment effect is maintained although may diminish slightly.[6]

The patient population of the CLEAR Serenity and supporting CLEAR Harmony, CLEAR Wisdom studies included only a minority of patients who were also receiving ezetimibe therapy. Unpublished results of post hoc subgroup analyses in patients on ezetimibe suggested that the reductions in LDL-C relative to placebo were smaller in patients receiving ezetimibe than not. However, the small numbers of patients and their post hoc nature mean these results should be interpreted with caution. In CLEAR Tranquility, where patients were all receiving additional ezetimibe, the treatment effect on LDL-C reduction was larger than with bempedoic acid without ezetimibe in other studies.[3]

There is very limited evidence on the efficacy of bempedoic acid in patients with HeFH (1.7% to 6.2% of patients in treatment groups across the CLEAR Serenity and supporting Harmony and Wisdom studies). In CLEAR Serenity and Tranquility, in patients statin intolerant, more patients appeared to be receiving treatment for primary prevention than secondary prevention (61% versus 39% in CLEAR Serenity and 25% of patients in CLEAR Tranquility reported a cardiac disorder at baseline). Subgroup analysis has suggested that the treatment effect of bempedoic acid on reducing LDL-C levels is consistent across primary and secondary prevention and in those with or without HeFH but due to the small patient numbers and lack of power, these results should be interpreted with caution.

Intolerance to statins was self-reported and this may be less robust than other methods. In addition, the definitions of statin intolerance may not reflect clinical practice. In CLEAR Serenity, statin intolerance was defined as being unable to tolerate at least two statins (one at low dose)

due to adverse effects. While in CLEAR Tranquility, statin intolerance was defined as attempting statin therapy and being unable to tolerate it due to an adverse effect. The latter definition is less clear and may allow inclusion of patients who have had a short trial of one statin only. Guidance from the Scottish Intercollegiate Guidelines Network (SIGN) states that there is evidence to suggest that the vast majority (70–90%) of patients who report prior statin intolerance (to one or more statins with discontinuation or myopathy or other apparent statin-related side effect) are able to take some form of statin when rechallenged. [2, 10]

There is no evidence that directly compares bempedoic acid plus ezetimibe, alirocumab with or without ezetimibe, and evolocumab with or without ezetimibe. The submitting company performed an NMA in statin intolerant patients but the results are uncertain due to the substantial heterogeneity across studies. This includes differences across studies in populations (baseline patient and disease characteristics), and definitions of statin intolerance. In addition, data used in the NMA were very limited for some treatments. The study populations included in the NMAs were broader than the submitting company's proposed positioning. There are SMC restrictions on the use of alirocumab and evolocumab in patients in Scotland and it is unclear what proportions of study patients included in the NMAs would have been eligible for PCSK9 inhibitor treatment according to these restrictions and if the results could be extrapolated to such patients in clinical practice.

The introduction of bempedoic acid would offer an additional oral lipid lowering treatment for patients who cannot tolerate or have contra-indications to statins. The submitting company has proposed that it is used in patients who are already taking ezetimibe.

Summary of comparative health economic evidence

The submitting company has proposed a product position for bempedoic acid that is narrower that its marketing authorisation and is seeking approval for the following two positions:

In combination with ezetimibe, in patients who are statin intolerant or for whom a statin is contraindicated, and ezetimibe alone does not appropriately control LDL-C and

- PCSK9 inhibitors are not appropriate (**position 1a**), or
- PCSK9 inhibitors are appropriate (**position 1b**)

For position 1a, the relevant comparator is ezetimibe. As part of the updated NMA for the resubmission, the comparators considered for position 1b were alirocumab plus ezetimibe and evolocumab plus ezetimibe.

The submitting company developed a Markov model over a lifetime time horizon to estimate cost effectiveness. The model included the following core health states on CV events: high risk for ACVD (patients without a prior CV event); myocardial infarction; unstable angina; stable angina; ischaemic stroke; and, transient ischaemic attack. To allow for changing risks, costs and, quality of

life in the few years after a CV event, the model also included post-event health states: 0 to 1-year post- CV event; 1 to 2-year post- CV event; and, >2 years post- CV event. The starting health state depends on the selected position for the analysis. No adverse events were included in the model.

The primary source of clinical data for bempedoic acid in the statin intolerant population was CLEAR Serenity and CLEAR Tranquility and these were used to inform the baseline characteristics, except for prior CV events, in the economic model.[2, 3] The distribution of prior CV event types at baseline were taken from Ward *et al*.[12] The submitting company modelled the positions 1a and 1b according to the predominant CV risk included in the CLEAR trials. Position 1a reflects a primary prevention population without HeFH and position 1b reflects a secondary prevention population without HeFH.

Different mean baseline LDL-C levels are applied in the model depending on which position is selected for the analysis. The baseline LDL-C levels (mmol/L) applied in position 1b (alirocumab and evolocumab appropriate) were taken from patients eligible for PCSK9 inhibitor treatment in the CLEAR studies. However, in position 1a (alirocumab and evolocumab not appropriate) baseline LDL-C levels were taken from all patients in the CLEAR trials with no distinction for PCSK9 inhibitor eligibility. The submitting company's justification for the baseline LDL-C used for position 1a was informed by clinical expert opinion from their Delphi panel[13] and NHS data[14], which suggested that most patients eligible for PCSK9 inhibitor treatment do not receive it.

The company conducted an NMA focussed on the statin intolerant population, to compare bempedoic acid plus ezetimibe with the comparators. The primary efficacy outcome of the NMA was percentage change from baseline LDL-C at 12 weeks and the results showed bempedoic acid plus ezetimibe was more effective than ezetimibe alone but less effective than alirocumab plus ezetimibe. Reduction in LDL-C was used as a surrogate outcome measure to estimate reduction in risk of future CV events. For the base-case analysis, data from the Cholesterol Treatment Trialists Collaboration (CTTC) meta-analysis[15] was used to estimate the rate at which the risk of a CV event declines with absolute reduction in LDL-C levels. The CTTC meta-analysis has been previously accepted in related health technology assessment (HTA) submissions to inform this relationship. [15]

Percentage change in LDL-C levels at 12 weeks is assumed to remain constant for the duration of the model time horizon or until the treatment is discontinued. Long-term data of evolocumab from a published study showed an annualised treatment discontinuation rate of 6.7%, which was used in the base case all treatments.[16]

Background CV risks for patients in position 1a (primary prevention) were based on QRISK3 (adjusted for the distribution of prior CV events in presented Ward *et al*.)[12] while background CV risks for patients in position 1b (secondary prevention) were taken from The Health Improvement Network (THIN) reported in the National Institute for Health and Care Excellence (NICE) submission for alirocumab (TA393).[17] The company also accounted for the increased risk associated with multiple CV events (a multiplier of 1.5 based on Smolina *et al.*[18]) and age (3% and 5% each year for non-fatal CV events and fatal cardiovascular events, respectively, based on

Wilson *et al*.[19]). The sources used to inform background CV risks have been previously accepted in NICE clinical guideline CG181[20] and related submissions to NICE and the SMC.

No health-related quality of life data were collected in the bempedoic acid studies. Instead, published utility data and regression calculations used to calculate per cycle health state utility values for all CV events except TIA were taken from Ara and Brazier[21]. Utility data for TIA was obtained from Luengo-Fernandez *et al*[22]. The submitting company modelled utility by applying an age-adjusted baseline utility (depending on the history of CVD) with multiplicative CV disutilities (dependent on the time since the CV event).

The costs considered in the model consist of drug acquisition costs, administration, and annual check-up costs for alirocumab and evolocumab, disease management costs, and, CV event management costs. To estimate CV event management costs, the company used CG181[20] and a published UK study which recorded first- and second- CV event related costs separately.[23]

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price of bempedoic acid. The company's base case results are presented in Table 2 for position 1a and Table 3 for position 1b. PAS discounts are in place for alirocumab and evolocumab and these were included in the results used for decision-making by using estimates of the comparator PAS prices. Key scenarios analyses are presented in Table ***4***.

The results presented do not take account of the PAS for alirocumab and evolocumab, but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company, which used an estimate of the PAS prices for alirocumab and evolocumab due to commercial confidentiality and competition law issues.

Table 2. Company's deterministic base case results, ICER – position 1a

Technologies	Total QALYs	Incremental (versus baseline)	ICER (£/ QALY)
		QALYs	List price
ezetimibe	8.92	-	-
bempedoic acid + ezetimibe	9.11	0.19	26,444
ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life-year.			

Table 3. Company's deterministic base case results, ICER – position 1b

Technologies	Total QALYs	Incremental (versus baseline)	ICER (£/ QALY)*
		QALYs	List price
bempedoic acid + ezetimibe	6.84	-	
alirocumab + ezetimibe	7.14	-0.30	85,163
evolocumab + ezetimibe	7.14	-0.30	86,370

ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life-year.
*ICERs presented are in the south-west quadrant of the cost-effectiveness plane and represent a cost-saving per QALY lost.

Table 4. Key scenario analyses

	Base case setting	Scenario	List price analysis ICERs (£/QALY)		
			Position 1a	Position 1b*	
			vs. ezetimibe	vs. alirocumab + ezetimibe	vs. evolocumab + ezetimibe
N/A	*Base case*	-	*26,444*	*85,163*	*86,370*
1	Baseline LDL-C level (1a)	Baseline LDL-C levels from patients ineligible for PCSK9 inhibitor treatment (with or without prior ezetimibe use)	27,431	N/A	
2	Baseline LDL-C level (1a)	Baseline LDL-C levels from all patients who received prior ezetimibe	29,886		
3	Baseline LDL-C level (1a)	Baseline LDL-C levels from patients who received prior ezetimibe and are ineligible for PCSK9 inhibitors	31,128		
4	Baseline LDL-C = (1b)	Baseline LDL-C level from patients who received prior ezetimibe and are eligible for PCSK9 inhibitor treatments	N/A	86,599	87,827
5	Lifetime treatment duration	Treatment duration capped at 5 years	25,877	89,166	90,416
6	Lifetime treatment duration	Treatment duration capped at 10 years	26,477	87,549	88,788
7	HeFH CV risk multiplier = 1	HeFH CV risk multiplier = 2	22,028	52,490	53,232
8	HeFH CV risk multiplier = 1	HefH Proportion from the trial HeFH CV risk multiplier = 2	26,189	83,864	85,053
9	Treatment discontinuation rate of 6.7% from long-term PCSK9 inhibitor trials	Treatment discontinuation rate of 9.4% from CLEAR Tranquility	26,106	83,870	85,058
10	Ischaemic stroke costs from Danese *et al*.[23]	Ischaemic stroke costs from TA393	25,735	85,446	86,654
11a	Base case	Position 1a - combination scenarios 3, 9 and 10	29,946	N/A	

11b	Base case	Position 1b - combination scenarios 4, 9 and 10	N/A	85,580	86,787

LDL-C = low-density lipoprotein cholesterol, HeFH = heterozygous familial hypercholesterolaemia, CV = cardiovascular, PCSK9 = proprotein convertase subtilisin/ kexin type 9, ICER: incremental cost-effectiveness ratio, QALY = quality-adjusted life-year

*ICERs presented are in the south-west quadrant of the cost-effectiveness plane and represent a cost-saving per QALY lost.

Key limitations

- The updated NMA informing the estimates of reduction in LDL-C better reflects the submitting company's positioning of bempedoic acid as it only includes a selected subgroup of patients receiving ezetimibe at baseline. However, the NMA is still subject to a high degree of clinical heterogeneity (specifically related to CV risk, presence of HeFH and PCSK9 inhibitor eligibility) that makes the overall conclusions of the analysis uncertain. Nonetheless, the data available may limit the ability of the submitting company to resolve these discrepancies.
- The model assumes that the treatment effect at week 12 is sustained over the lifetime of the model, despite the mean treatment duration being less than this. However, scenarios capping treatment duration (a proxy for duration of treatment benefit) to 5 and 10 years did not have a substantial impact on the ICER.
- The submitting company modelled baseline LDL-C levels in position 1a (PCSK9 inhibitors inappropriate) from all patients (i.e. patients eligible and ineligible for PCSK9 inhibitors) based on the assumption that the minority of the patients fulfilling the PCSK9 inhibitor treatment criteria currently receive PCSK9 inhibitors. The New Drugs Committee thought that the submitting company's approach can be considered appropriate for the Scottish context. Nonetheless, a scenario for position 1a was explored using baseline LDL-C levels for patients who are ineligible for PCSK9 inhibitors and this had a marginal impact on the ICER.
- The submitting company provided scenarios exploring baseline LDL-C levels from patients with and without prior ezetimibe use, which had a marginal impact on the ICER. To reflect the intended positioning, baseline LDL-C levels from patients with prior ezetimibe use would be more appropriate to inform the model. However, the full study population of CLEAR Serenity does not reflect the prior ezetimibe population in which the submitting company is positioning bempedoic acid and as such limits the reliability of these analyses.
- In the original submission, subgroup analyses varying CV risk (primary prevention, and secondary prevention or HeFH), assuming the treatment effect is similar in people with/without HeFH and with/without CVD, and different baseline LDL-C levels, were explored by the submitting company upon request. However, subgroup analyses were not presented for the resubmission. For the subgroups, baseline LDL-C levels and CV risks did differ from the modelled populations. The Committee's preference was aligned with the submitting company's modelled population and as such, the base case approach can be considered appropriate.
- The majority of the clinical evidence for the position 1a and 1b (statin intolerant population) is for patients without HeFH and the submitting company's base case results reflect this

population. However, CV risks are expected to be greater in patients with HeFH than patients without HeFH. Analyses exploring a HeFH CV risk multiplier of 2 for the HeFH only population had a substantial impact on the ICERs. However, in Scottish clinical practice, genetic testing for HeFH may be limited and may affect only a small proportion of the patient population. Robust exploration of the HeFH only subgroup is subject to data limitations and remains an unresolvable uncertainty.

- The combined scenario presented in
- Table ***4***, which incorporates baseline LDL-C levels for prior ezetimibe use and PCSK9 inhibitor eligibility, discontinuation rate of 9.4% from CLEAR Tranquility and IS costs based on TA393, represents a plausible alternative to the submitting company's ICERs for position 1a and 1b. However, as mentioned previously, there are limitations around the estimates of baseline LDL-C levels for patients with prior ezetimibe and for patients who are ineligible for PCSK9 inhibitors.

Despite the limitations outlined above, the Committee considered the economic case for use of bempedoic acid in position 1a has been demonstrated.

Summary of patient and carer involvement

No patient group submission was received.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published a clinical guideline (CG181) on cardiovascular disease risk assessment and reduction, including lipid modification in July 2014 and this was last updated in September 2016.[9] In patients with established CVD, including acute coronary syndrome, statins are recommended at the maximum tolerable dose (atorvastatin 80mg). Specialist advice should be sought when patients with a high risk of CVD (primary or secondary) are intolerant to three different statins. Fibrates, nicotinic acid, bile sequestrants and omega-3 fatty compounds are not recommended as monotherapy or in combination with a statin for people being treated for primary or secondary CVD, those with CKD or type I or type II diabetes. In people with primary (heterozygous-familial and non-familial) hypercholesterolaemia, ezetimibe can be taken as monotherapy when statins are contraindicated or not tolerated, or in combination with the person's usual statin when cholesterol target levels have not been met despite increased statin dose or where increased statin dose is intolerable.

NICE published a clinical guideline (CG71) on the identification and management of familial hypercholesterolaemia in August 2008 and this was last updated in October 2019.[24] The guideline recommend life-long lipid lowering treatment. A high-intensity statin with the lowest acquisition cost treatment is the recommended initial treatment for all adults with familial

hypercholesterolaemia. The maximum licensed/tolerated dose of statin should be considered to achieve a >50% reduction in LDL-C concentration from baseline. Ezetimibe monotherapy is recommended as an option for patients with primary heterozygous familial hypercholesterolaemia who have a contra-indication or cannot tolerate to statins. Ezetimibe, co-administered with initial statin therapy, is recommended as an option for the treatment of adults with primary heterozygous familial hypercholesterolaemia who have been initiated on statin therapy when serum total cholesterol or LDL-C concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy, and consideration is being given to changing from initial statin therapy to an alternative statin. NICE recommends that adults with familial hypercholesterolaemia should be offered a referral to a specialist when the recommended reduction in LDL-C concentration of >50% from baseline has not been achieved despite maximum tolerated dose of a high intensity statin and ezetimibe, the patient has been assessed as being at very high risk for of a coronary event (established coronary heart disease, family history or premature coronary heart disease or two or more other cardiovascular risk factors), or statin or ezetimibe therapy is contraindicated or not tolerated. Treatment with a bile acid sequestrant, nicotinic acid or a fibrate may be considered when statins or ezetimibe are contraindicated or not tolerated; the decision to offer these treatments should be made by specialists in familial hypercholesterolaemia.

The Scottish Intercollegiate Guidelines Network (SIGN) published publication on risk estimation and the prevention of cardiovascular disease includes recommendations on lipid lowering in June 2017.[10] This recommends atorvastatin 20mg/day is recommended as primary prevention in adults assessed as being at high cardiovascular risk, but with no established CVD, following an informed discussion on risks and benefits. In patients with established atherosclerotic cardiovascular disease, atorvastatin 80mg/day is recommended, with a lower dose considered for patients at increased risk of adverse events or drug interactions. Patients reporting statin intolerance can be rechallenged, if willing, initially with the same dose of the same statin unless they have significant creatine kinase elevation. An alternative statin should be offered if statin intolerance persists. People with familial hypercholesterolaemia should be offered statin therapy regardless of their calculated cardiovascular risk and may be considered for combination therapy with ezetimibe where LDL-C lowering is inadequate on maximally tolerated statin therapy, or for monotherapy when statins are contra-indicated. Patients with heterozygous familial hypercholesterolaemia and elevated LDL-C despite statin monotherapy or statin/ezetimibe combination therapy should be considered for a PCSK9 inhibitor. Ezetimibe and bile acid sequestrant therapy should only be considered for primary prevention in patients at elevated CVD risk in whom statin therapy is contraindicated, and in patients with familial hypercholesterolaemia. Ezetimibe and bile acid sequestrant therapy should be considered for secondary prevention in combination with maximum tolerated statin therapy if LDL cholesterol is considered to be inadequately controlled. Fibrates are not routinely recommended for primary or secondary prevention of cardiovascular disease.

The Joint British Societies produced consensus recommendations for the prevention of

cardiovascular disease in 2014 (JBS3).[25] Cholesterol lowering therapy is recommended in the individuals with established cardiovascular disease, high risk of cardiovascular disease: diabetes age >40 years, chronic kidney disease stages 3 to 5, or familial hypercholesterolaemia, high 10-year cardiovascular disease risk (threshold to be defined by NICE guidance), or high lifetime cardiovascular disease risk (JBS3 calculator) where lifestyle changes are insufficient. In all patients with familial hypercholesterolaemia, lifetime lowering of LDL-C is recommended to reduce CVD outcomes. Familial combined hyperlipidaemia cases should be managed by a lipid specialist. Statins are recommended as a highly effective treatment and, with benefits evident at 2mmol/L LDL-C levels, intensive therapy is encouraged. JBS3 advises a 'lower is better' approach, supporting strategies to achieve non-HDL-C of <2.5mmol/L (equivalent to LDL of <1.8mmol/L) in those at high risk of cardiovascular events. Combination therapy with the addition of a bile sequestrant, ezetimibe or possibly nicotinic acid to statin therapy are suggested when increased statin dose is not tolerated. However, specialist lipid advice should be sought if there is a failure to establish statin therapy in patients with established CVD or with suspected FH, or if there is a rise in creatine kinase >5× upper limit of normal on a statin. This guideline predates the availability of PCSK9 inhibitors and bempedoic acid.

Additional information: comparators

Ezetimibe and the PCSK9 inhibitors, alirocumab and evolocumab.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Bempedoic acid	**180mg orally once daily**	**721**

Costs from BNF online on 02 April 2021. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 8,518 patients eligible for treatment with bempedoic acid in year 1 and 8,614 in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 14 May 2021.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.