Healthcare Improvement Scotland | SMC Advice on new medicines

www.scottishmedicines.org.uk

SMC2292

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

Daiichi Sankyo UK Ltd

06 November 2020

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 full submission

bempedoic acid (Nilemdo®) is not recommended for 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 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.

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

The submitting company did not present sufficiently robust clinical and economic analyses to gain acceptance by SMC.

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.

Dosing Information

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

When bempedoic acid is co-administered with simvastatin, simvastatin dose should be limited to 20mg daily (or 40mg daily for patients with severe hypercholesterolaemia and high risk for cardiovascular complications, who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks).[1]

Product availability date

September 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-C in the blood. Additionally, inhibition of ACL by ETC-1002-CoA results in concomitant suppression of hepatic fatty acid biosynthesis.[1, 2]

The submitting company has requested that SMC considers the use of bempedoic acid in patients with primary hypercholesterolaemia or mixed dyslipidaemia when positioned:

- In combination with ezetimibe in patients who are statin-intolerant or for whom a statin is contra-indicated
- In combination with a statin and ezetimibe in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin.

Four randomised, double-blind phase III studies compared bempedoic acid with placebo in patients with primary hypercholesterolaemia and mixed dyslipidaemia. Two studies were performed in patients also receiving the maximum tolerated dose of a statin (CLEAR Harmony and

CLEAR Wisdom) and two in patients who were intolerant of statins (CLEAR Serenity and CLEAR Tranquility). In CLEAR Tranquility, all patients also received ezetimibe.

In CLEAR Harmony and CLEAR Wisdom, eligible patients were aged ≥18 years with heterozygous familial hypercholesterolaemia (HeFH) or a high cardiovascular risk with atherosclerotic cardiovascular disease or both. Atherosclerotic cardiovascular disease included established coronary heart disease (CHD): at least one of myocardial infarction, silent myocardial infarction, unstable angina, coronary revascularisation procedure, or clinically significant CHD diagnosed by invasive or non-invasive testing) or CHD risk equivalents (at least one of either peripheral arterial disease, previous ischaemic stroke with a focal ischaemic neurological deficit that persisted ≥ 24 hours). Patients had been receiving stable doses of maximally tolerated statin alone or in combination with other lipid-lowering therapies for ≥4 weeks prior to screening. They had a fasting LDL-cholesterol level of ≥70mg/dL (1.8mmol/L) during the 2-week screening period (CLEAR Harmony) or ≥100mg/dL (2.6mmol/L) at first screening and ≥70mg/dL (1.8mmol/L) one week before randomisation (CLEAR Wisdom).

In CLEAR Serenity and CLEAR Tranquility, eligible patients were aged ≥18 years, requiring additional lipid-lowering therapy for primary or secondary prevention of cardiovascular 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 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.[2-6]

In all four 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 52 weeks in CLEAR Harmony and Wisdom, for 24 weeks in CLEAR Serenity and for 12 weeks in CLEAR Tranquility. Randomisation was stratified by presence or absence of HeFH (CLEAR Harmony, Wisdom and Serenity), by intensity of baseline statin therapy: low, moderate or high (CLEAR Harmony and Wisdom) and by primary or secondary prevention (CLEAR Serenity).[2-6]

The primary efficacy outcome in all studies was the percentage change in LDL cholesterol from baseline to week 12. In CLEAR Harmony the primary outcome assessed safety, with efficacy assessed as a secondary outcome, and this was the key efficacy outcome. The primary efficacy outcome of percentage reduction in LDL-C from baseline to 12 weeks was significantly greater with bempedoic acid compared with placebo across all four 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 the four studies as detailed in Table 1.

Table 1: Results for primary and key secondary efficacy outcomes of the four CLEAR studies[2-6]

	Patients on maximum tolerated dose of statins				**Patients with a history of statin intolerance**			
	CLEAR Harmony		**CLEAR Wisdom**		**CLEAR Serenity**		**CLEAR Tranquility**	
	BA (n=1488)	**Placebo (n=742)**	**BA (n=522)**	**Placebo (n=257)**	**BA (n=234)**	**Placebo (n=111)**	**BA (n=181)**	**Placebo (n=88)**
Primary efficacy outcome								
Baseline LDL-C (mg/dL)	103.6	102.3	119.4	122.4	158.5	155.6	129.8	123.0
LS Mean % change in LDL-C	-16%	1.6%	-15%	2.4%	-23%	-1.2%	-24%	5.0%
LS mean difference (95% CI)	-18% (-20 to -16) p<0.001		-17% (-21 to -14 p<0.001		-21% (-25 to -18) p<0.001		-28% (-34% to -22%) p<0.001	
Secondary efficacy outcomes: LS Mean % change in:								
LDL-C (24wk), %	-15	1.2	-12	2.7	-21	-2.3	N/A	N/A
LS mean difference (95% CI)	-16% (-18 to -14) p<0.001		-15% (-20 to -10) p<0.001		-19 (-23 to -15) p<0.001		-	
Non-HDL-C (12wk), %	-12	1.5	-11	2.3	-18	-0.1	-18	5.2
LS mean difference (95% CI)	-13 (-15 to -12) p<0.001		-13.0 (-16 to -9.8) p<0.001		-18 (-21 to -15) p<0.001		-24 (-29 to -18) p<0.001	
TC (12wk), %	-10	0.8	-9.9	1.3	-15	-0.6	-15	2.9
LS mean difference (95% CI)	-11 (-12 to -9.8) p<0.001		-11(-14 to -8.8) p<0.001		-15 (-17 to -12) p<0.001		-18 (-22 to -14) p<0.001	
BA: bempedoic acid, LS: least squares, CI: confidence interval, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TC: total cholesterol								

An open-label extension study to CLEAR Harmony (study 1002-050) was designed primarily to assess safety and efficacy to week 78 as secondary outcomes. This ongoing phase III study has enrolled 1462 patients who completed CLEAR Harmony (970 originally randomised to bempedoic acid and 492 to placebo) who are to receive bempedoic acid 180mg daily. Published results are available to week 52 of the extension for 288 patients originally randomised to bempedoic acid and 131 patients to placebo and the mean percentage change in LDL-C from baseline was -16% and -17% respectively.[2, 7]

The proposed positioning by the company for the use of bempedoic acid is with ezetimibe. In CLEAR Harmony, CLEAR Wisdom and CLEAR Serenity only small proportions of study patients received ezetimibe (7.7%, 8.0% and 14% respectively). All patients in the CLEAR Tranquility study received ezetimibe in addition to study medication. Published results from pooled subgroup analyses of CLEAR Harmony and CLEAR Wisdom (in patients on maximum tolerated statin dose) found a difference in percentage change in LDL-C from baseline to 12 weeks of -13% (95% CI: -20% to -6.2%) between bempedoic acid (n=144) and placebo (n=73) in the subgroup of patients who were also taking ezetimibe at baseline and -19% (95% CI:-21% to -17%) between bempedoic acid (n=1778) and placebo (n=905) in the subgroup of patients who were not taking ezetimibe at baseline. Pooled subgroup analyses of CLEAR Serenity and CLEAR Tranquility (in patients with statin intolerance) found a difference in percentage change in LDL-C from baseline to 12 weeks of -28% (95% CI: -33% to -22%) between bempedoic acid (n=207) and placebo (n=97) in the subgroup of patients who were also taking ezetimibe at baseline and -23% (95% CI:-26% to -19%) between bempedoic acid (n=192) and placebo (n=92) in the subgroup of patients who were not taking ezetimibe at baseline.[8]

The company performed two network meta-analyses (NMAs) to compare bempedoic acid and bempedoic acid plus ezetimibe with ezetimibe, alirocumab and evolocumab in adult patients with hyperlipidaemia at moderate or high risk of or with atherosclerotic cardiovascular disease who require further lipid-lowering therapy despite statin treatment at the maximally tolerated dose or who are considered statin intolerant. One NMA was performed in patients who were statin intolerant and one in patients on maximum tolerated dose of statin. The NMAs included a total of 31 studies and compared treatments using the percentage change in LDL-C levels from baseline to week 12.

In the statin intolerant NMA, the results indicated that there was no evidence of a difference between bempedoic acid and ezetimibe and significantly less of a reduction in percentage change in LDL-C from baseline to week 12 with bempedoic acid when compared with bempedoic acid plus ezetimibe, alirocumab and evolocumab. The NMA results indicated that there was no evidence of a difference between bempedoic acid plus ezetimibe (proposed positioning) compared with alirocumab and evolocumab and significantly more of a reduction in percentage change in LDL-C from baseline to week 12 with bempedoic acid plus ezetimibe when compared with bempedoic acid and ezetimibe each individually. However, the company noted that the results should be interpreted with caution due to the high level of heterogeneity across included studies.

In the maximum tolerated statin NMA, the results indicated that there was no evidence of a difference between bempedoic acid and ezetimibe or bempedoic acid plus ezetimibe combination and that there was significantly less of a reduction in percentage change in LDL-C from baseline to week 12 with bempedoic acid when compared with alirocumab and evolocumab. The NMA results indicated that there was significantly less of a reduction in percentage change in LDL-C with bempedoic acid plus ezetimibe (proposed positioning) compared with alirocumab and evolocumab.

Summary of evidence on comparative safety

A pooled safety analysis has been reported for the four phase III 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.[2, 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% vs 0.7%) or musculoskeletal and connective tissue disorders when used in addition to statins (2.8% vs 1.9%).[2, 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%).[2, 8]

Summary of clinical effectiveness issues

Statins are the treatment of choice for patients with hypercholesterolaemia. However, a proportion of patients fail to achieve adequate LDL-C control despite maximum tolerated doses of statins and require additional lipid-lowering therapy. In addition, a further 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.[2, 9, 10] The company has proposed that bempedoic acid is

considered for use in combination with ezetimibe and therefore the only available alternative treatments are the PCSK9 inhibitors when patients meet their restrictions for use defined by SMC. For many patients there are no other suitable alternative treatments.

The percentage reduction in LDL-C was statistically significantly larger with bempedoic acid compared with placebo across all four key CLEAR studies and this was supported by significantly greater improvements in secondary outcomes. In CLEAR Harmony and Wisdom, in patients who were receiving maximum tolerated doses of statins, the placebo-corrected percentage reduction in LDL-C was smaller, with a moderate reduction in LDL-C of 17% to 18% compared with reductions of 21% to 28% in the CLEAR Serenity and Tranquility studies, in patients who were intolerant of statins. This may be due to lower LDL-C baseline levels and the possible diminished effect due to inhibition in the similar pathway of bempedoic acid and statins. The European Medicines Agency (EMA) noted that the capacity to lower LDL-C declined with the highest doses of background statin therapy. However, despite this lower reduction in LDL-C, this was considered to be clinically relevant by the EMA.[2-6]

The primary efficacy outcome, mean percentage change in LDL-C is accepted as a surrogate endpoint for the reduction of cardiovascular events but published CLEAR studies have not assessed the effect of bempedoic acid on cardiovascular outcomes. An ongoing CLEAR OUTCOMES study will assess a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke or coronary revascularisation in more than 14,000 patients with a history or high risk of cardiovascular disease, who were statin-intolerant and fasting LDL-C of ≥100 mg/dL (2.6mmol/L). This study is not expected to be completed until December 2022.[11]

In all 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 (to -15% and -16% in CLEAR Harmony and Wisdom and to -19% in CLEAR Serenity). Results to 52 weeks are available for CLEAR Harmony and Wisdom where the difference in percentage reduction in LDL-C were -13% and -12% respectively. The slight decrease in effect may be a result of permitted changes of the background therapy after 24 weeks, which occurred in 9.2% of the patients in CLEAR Harmony and Wisdom, and was slightly less intensified in the bempedoic acid than the placebo group (8.8% vs 10%).[2]

The patient populations of the CLEAR Harmony, CLEAR Wisdom and CLEAR Serenity studies included only a minority of patients who were also receiving ezetimibe therapy and, therefore, the New Drugs Committee felt that there was limited evidence to support the positioning proposed by the company. Subgroup analyses across studies indicated some differences in treatment effect in some subgroups and was higher in females than males and for different BMI categories and was lower with increased statin intensity. There also appeared to be a lower treatment effect relative to placebo when bempedoic acid was used on a background of ezetimibe therapy but this was not significant.[2] 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 Harmony, Wisdom and Serenity studies). In addition, the majority of study patients in CLEAR Harmony and Wisdom had atherosclerotic disease (≥94%) and were receiving treatment for secondary prevention. Therefore, the proportion of patients, receiving the maximum tolerated dose of statin, who were receiving bempedoic acid for primary prevention was very limited. In CLEAR Serenity and Tranquility, in patients intolerant of statins, 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). However both of these studies included smaller numbers of patients and so across all four studies, the proportion of patients receiving primary prevention was low. 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.

There are a number of other limitations in the CLEAR studies including a run-in period of 2 weeks in CLEAR Harmony which is short to exclude possible confounding from background therapy. The number of patients included in CLEAR Serenity and CLEAR Tranquility (intolerant to statins population) was limited to 346 and 269 patients respectively. Intolerance to statins was self-reported by the patient 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. [3, 5, 9] In CLEAR Harmony and Wisdom, the maximum tolerated dose of statins was determined by the investigator and therefore may allow variability in definition and may not reflect clinical practice.[4, 6]

The baseline LDL-C levels required for study inclusion varied across the studies and was lowest in CLEAR Harmony where eligible patients were required to have an LDL-C level ≥70 mg/dL (1.8mmol/L) at screening while on stable maximum tolerated statin dose. Although this LDL-C level may not define hypercholesterolaemia, the EMA considered that these patients would likely have had hypercholesterolaemia when they started statin therapy in the past and the baseline mean LDL-C level exceeded this at 103.2mg/dL (2.7mmol/L).[2, 6]

For patients who are already receiving the maximum tolerated dose of statins or are unable to tolerate them there are limited treatment options. PCSK9 inhibitors may be an option for a small proportion of patients who meet SMC criteria for their use. Stable doses of PCSK9 inhibitors were only permitted to continue during CLEAR Wisdom and Serenity and could be added after week 24 in CLEAR Harmony and Wisdom if the LDL-cholesterol was ≥170mg/dL (4.4mmol/L), although reported use was very small.[3, 5 4, 6]

There is no evidence that directly compares bempedoic acid with ezetimibe, alirocumab and evolocumab. The company performed NMAs in statin intolerant and the maximum tolerated dose of statin populations but the results are highly uncertain due to the substantial heterogeneity across studies. This includes differences across studies in methods, study populations (baseline patient and disease characteristics), use of concomitant treatment, time of assessment and definitions of statin intolerance and maximum tolerated statin dose. In addition, data used in the NMA were very limited for some treatments, particularly bempedoic acid plus ezetimibe. The study populations included in the NMAs were broader than the company's proposed positioning, and patients were not required to be taking ezetimibe. There are clear 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. This may further reduce LDL-C in patients who are already receiving the maximum tolerated dose of statins or offer an alternative treatment option for patients who cannot tolerate or have contra-indications to statins. In both populations, the company has proposed that it is used in patients who are already taking ezetimibe but there is limited evidence to support this. The effect of bempedoic acid treatment on cardiovascular outcomes remains to be demonstrated from the CLEAR Outcomes study.

Summary of comparative health economic evidence

The two positions discussed in the clinical sections above are split into groups "a" and "b" for the economic analysis due to different comparators. In position 1a PCSK9 inhibitors (alirocumab or evolocumab) are not appropriate (the comparator is ezetimibe) while position 1b and 2b relate to situations when PCSK9 inhibitors are appropriate (the comparators are alirocumab and evolocumab). To summarise, the three groups considered in the economic analysis within the company's proposed positioning are:

- 1a: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are not appropriate;
- 1b: When statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate; and,
- 2b: When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and alirocumab and evolocumab are appropriate.

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 cardiovascular events: high risk for atherosclerotic cardiovascular disease (patients without a prior cardiovascular 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 cardiovascular event, the model also included post-event health states: 0 to 1-year post-cardiovascular event; 1 to 2-year post-cardiovascular event; and, >2 years post-cardiovascular event. The starting health state depends on the selected position for the analysis. No adverse events were included in the model.

The CLEAR studies were used to inform the baseline characteristics in the model. In the base case, it is assumed that all patients were in primary prevention without HeFH in position 1a and in secondary prevention without HeFH in positions 1b and 2b. This assumption was made as most patients in the CLEAR studies had a similar history of prior cardiovascular events and HeFH.

Different mean baseline LDL-C levels are also applied in the model depending on which position is selected for the analysis. The baseline LDL-C levels (mmol/L) applied in positions 1b and 2b (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) LDL-C levels were taken from all patients in the CLEAR studies as the submitting company assumed that most patients eligible for PCSK9 inhibitor treatment do not receive it in clinical practice. This was based on clinical expert opinion from the submitting company's Delphi panel and NHS data.[12, 13] The distribution of prior cardiovascular event types at the start of the model (the secondary prevention population) were taken from UK registry data (Ward *et al.* 2007) as this data was not available from the CLEAR studies.[14]

The model effect was worked through using LDL-C as a surrogate outcome measure linked to cardiovascular events, where reducing LDL-C is predicted to reduce cardiovascular events in the future. For the base-case analysis, the company chose the Cholesterol Treatment Trialists Collaboration (CTTC) meta-analysis to provide the rate at which the risk of a cardiovascular event declines with the 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]

The company conducted two NMAs in order to compare bempedoic acid with the comparators and the outcome used was percentage change from baseline LDL-C at 12 weeks. The treatment effect observed in LDL-C 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 discontinuation rate of 6.7% and the company assumed this discontinuation rate for all treatments in the base case.[16]

Background cardiovascular risks for primary prevention patients were based on QRISK3 (adjusted for the distribution of prior cardiovascular events in Ward *et al*. 2007) while background cardiovascular risks for secondary prevention patients were taken from The Health Improvement Network (THIN) reported in the National Institute for Health and Care Excellence (NICE) submission for alirocumab (TA393). The company also accounted for the increased risk associated with multiple cardiovascular events (a multiplier of 1.5 based on Smolina *et al.* 2012) and age (3% and 5% each year for non-fatal cardiovascular events and fatal cardiovascular events respectively, based on Wilson *et al*. 2012.[17, 18] These sources used to inform background cardiovascular risks have been previously accepted in either NICE clinical guideline CG181 or related submissions to NICE and the SMC.

No health-related quality of life data were collected in the bempedoic acid studies. As such, these data were taken from the studies identified in the company's systematic literature review.[19, 20] In these studies, EQ-5D responses were converted into utilities using time trade-off UK population tariffs. The submitting company then modelled utility by applying an age-adjusted baseline utility (depending on the history of cardiovascular disease) with multiplicative cardiovascular disutilities (depending on the time since the cardiovascular event).

The costs considered in the model consist of drug acquisition costs, annual check-up costs for alirocumab and evolocumab, disease management costs, and, cardiovascular event management costs. To estimate cardiovascular event management costs, the company used CG181 and a published UK study in the base case. This study recorded first and second cardiovascular event related costs separately.[21]

The company's main economic results are given in Table 2 using list prices. The results presented do not take account of the patient access scheme (PAS) for alirocumab and evolocumab and when an estimate of the PAS was included, bempedoic acid became less cost-effective. 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.

Using list prices, the incremental cost-effectiveness ratio (ICERs) for bempedoic acid compared with ezetimibe are £25,812 and £67,621 in position 1a (alirocumab and evolocumab not appropriate). In positions 1b and 2b (alirocumab and evolocumab appropriate) bempedoic acid generates fewer QALYs but also less cost compared to alirocumab and evolocumab, resulting in ICERs in the south-west quadrant of the cost-effectiveness plane. In these situations, the ICER represents the cost saving per QALY lost and an ICER above the willingness to pay threshold could be considered cost effective.

Table 2. Company's deterministic base case results, ICER

				Incremental (versus baseline)			ICER (£/ QALY)	
Technologies	**Total costs (£)**	**Total Lys**	**Total QALYs**	**Costs (£)**	**Lys**	**QALYs**	**Fully incremental**	**Versus baseline**
Position 1a								
EZE	7,154	12.08	9.05	-	-	-	-	-
BA + EZE	12,155	12.30	9.24	5,001	0.22	0.19	25,812	25,812
Position 1b								
BA +EZE	17,482	10.39	7.02	-	-	-	-	-
ALI	42,877	10.47	7.08	25,395	0.08	0.06	421,476	421,476
EVO	43,315	10.51	7.11	25,834	0.12	0.09	15,303	290,653
Position 2b								
BA + EZE	17,025	9.78	6.58	-	-	-	-	-
ALI	41,867	10.07	6.80	24,843	0.29	0.21	116,143	116,143
EVO	42,629	10.28	6.95	25,605	0.50	0.36	5,083	70,384

ALI: alirocumab, BA: bempedoic acid, EVO: evolocumab, EZE: ezetimibe, ICER: incremental cost-effectiveness ratio, LY: life-year, QALY: quality-adjusted life-year.

From the submitting company's one-way sensitivity analysis, results were most sensitive to the annual acquisition cost of treatment, the treatment effect (reduction in LDL-C), the baseline LDL-C and the discontinuation rate. The utility multiplier for the starting health state (high risk for atherosclerotic cardiovascular disease) was also a key driver in position 1a. Except for changes to the annual acquisition costs of alirocumab and evolocumab (which are subject to a PAS), the net monetary benefit increased or decreased by less than £1,000 in each position.

Subgroup analysis varying cardiovascular disease risk are given in Table 3 and are conducted on the assumption that the treatment effect on LDL-C is similar in people with/without HeFH and with/without cardiovascular disease. The submitting company's key scenario analysis are given in

Table *4* and Table 5 and relate to baseline LDL-C levels and the duration of treatment.

Table 3. Subgroup results analyses based on cardiovascular risk – ICER versus comparators

Population^	**ICER**	
	Statin intolerant population (position 1)	**Maximum tolerated statin population (position 2)**
Without CVD	EZE: £25,258	-
Without CVD, HeFH	ALI: £385,659* EVO: £266,825*	ALI: £100,847* EVO: £62,439*
With CVD (high risk or very high risk)	LDL-C=any EZE: £31,755	-
	LDL-C>2.5 EZE: £22,262	-
	LDL-C>3.0 EZE: £20,285	-
	LDL-C>3.5 EZE: £16,002	-
With CVD, high risk, Non-HeFH	ALI: £373,496* EVO: £257,828*	ALI: £102,548* EVO: £62,462*
With CVD, very high risk, Non-HeFH	ALI: £415,890* EVO: £286,725*	ALI: £117,625* EVO: £71,148*
With CVD, high or very high risk, HeFH	EZE: £40,005	-
With CVD, high or very high risk, HeFH	ALI: £413,882* EVO: £285,634*	ALI: £108,499* EVO: £65,965*

ALI: Alirocumab, BA: bempedoic acid, CVD: cardiovascular disease, EVO: Evolocumab, EZE: ezetimibe, HeFH: heterozygous familial hypercholesterolaemia, ICER: incremental cost-effectiveness ratio, LDL-C: Low-density lipoprotein cholesterol.

*ICERs in the south-west quadrant of the cost-effectiveness plane (i.e. BA generates fewer QALYs and less cost than ALI and EVO).

^Estimated by changing baseline characteristics in the model (primary/secondary prevention, with/without HeFH, proportion of recurrent CV events and baseline LDL-C)

Table 4. Scenario analyses based on LDL-C levels – ICER versus comparators

	Position 1a	Position 1b	Position 2b
Base case results	EZE: 25,812	ALI: 421,476* EVO: 290,653*	ALI: 116,143* EVO: 70,384*
Baseline LDL-C levels from patients ineligible for PCSK9 inhibitor treatment (with or without prior EZE use)			
Results	EZE: 26,696	NA	NA
Baseline LDL-C level from patients who received prior EZE and are eligible for PCSK9 inhibitor treatments			
Results	NA	ALI: 428,457* EVO: 295,440*	ALI: 106,674* EVO: 64,853*
Baseline LDL-C level from all patients who received prior ezetimibe			
Results	EZE: 28,887	NA	NA
Baseline LDL-C level from patients who received prior EZE and are ineligible for PCSK9 inhibitor treatments			
Results	EZE: 29,999	NA	NA
ALI: alirocumab, BA: bempedoic acid, EVO: evolocumab, EZE: ezetimibe, ICER: incremental cost effectiveness ratio, LDL-C: Low-density lipoprotein cholesterol (mmol/L), NA: not applicable. *ICERs in the south-west quadrant of the cost-effectiveness plane (i.e. bempedoic acid generates less QALYs and less costs than ALI and EVO).			

Table 5. Scenario analyses based on duration of treatment – ICER versus comparators

Position 1a	Position 1b	Position 2b
Base case: lifetime		
EZE: 25,812	ALI: 421,476* EVO: 290,653*	ALI: 116,143* EVO: 70,384*
Treatment duration capped at 5 years		
EZE: 26,145	ALI: 450,623* EVO: 311,290*	ALI: 121,544* EVO: 74,364*
Treatment duration capped at 10 years		
EZE: 26,318	ALI: 438,106* EVO: 302,400*	ALI: 119,259* EVO: 72,610*
ALI: alirocumab, BA: bempedoic acid, EVO: evolocumab, EZE: ezetimibe, ICER: incremental cost effectiveness ratio. *ICERs in the south-west quadrant of the cost-effectiveness plane (i.e. BA generates less QALYs and less costs than ALI and EVO).		

Key limitations

- The NMA results provided by the company are uncertain, principally due to the extent of the clinical and statistical heterogeneity observed from the studies included in the networks and lack of evidence for bempedoic acid in patients with prior ezetimibe. If bempedoic acid is to be used after ezetimibe, as an add on treatment rather than a

replacement for ezetimibe, the studies in the NMA should have been restricted to those in patients on prior and concomitant ezetimibe. As such, the company's cost effectiveness estimates must be interpreted with caution.

- There are discrepancies between the study populations informing the NMAs and the modelled positions. Not all patients in the studies included in the NMA supporting the data for positions 1b and 2b are derived from study populations without HeFH in secondary prevention. Additionally, not all patients in the NMA supporting that data for position 1a are derived from study populations without HeFH in primary prevention. Furthermore, positions 1b and 2b (situations when alirocumab or evolocumab are appropriate) are not informed by networks of studies that reflect only patients eligible for PCSK9 inhibitors. Additionally, position 1a (when alirocumab or evolocumab are not appropriate) are not informed by networks of studies that reflect only patients ineligible for PCSK9 inhibitors. However, the data available in the comparator studies limits the ability of the submitting company to resolve these discrepancies.
- The submitting company modelled baseline LDL-C levels in position 1a (when alirocumab and evolocumab are not appropriate) from all patients (i.e. patients eligible and ineligible for alirocumab and evolocumab) based on the assumption that the minority of the patients fulfilling the PCSK9 inhibitor treatment criteria currently receive PCSK9 inhibitor treatment. To test this assumption, the submitting company was asked to explore scenarios using LDL-C levels from patients ineligible for PCSK9 inhibitor treatment in position 1a. If the submitting company's assumption is unreasonable, the company is potentially overestimating the cost-effectiveness of bempedoic acid compared to ezetimibe.
- 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. Furthermore, the secondary outcome of LDL-C reduction to week 24 has indicated that the bempedoic acid treatment effect may diminish slightly. However, the duration of treatment or magnitude of treatment waning may be different across the different treatments under consideration and therefore it is not possible to predict the direction of any bias. To explore this uncertainty, using the minimum number of assumptions, the submitting company was asked to apply treatment durations of 10 and 5 years (to all treatments). However, the impact on the results was relatively small in each position.
- According to clinical experts and a previous related submission to NICE, patients with HeFH have a far greater risk of cardiovascular disease than patients without HeFH. Thus, applying multiplier of 1 to cardiovascular risks in the subgroup of patients with HeFH is inappropriate and underestimating the cost effectiveness of more effective treatments in this subgroup. The company subsequently provided sensitivity analysis which increased the multiplier but only to 1.5, which was not enough to fully test the sensitivity of the model to changes in this parameter.

Due to the limitations outlined above the economic case has not 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.[10] NICE recommend atorvastatin 20mg daily for primary prevention of cardiovascular disease in the following groups:

- ≥10% ten year risk of developing CVD (QRISK2 tool)
- Type I diabetes who are over the age of 40, have had diabetes >10 years, have established neuropathy or have other CVD factors
- Type II diabetes who have ≥10% ten year risk of developing CVD (QRISK2 tool)
- Chronic kidney disease

NICE also recommends that atorvastatin 20mg may also be considered in:

- People ≥85 years old (possible reduction in non-fatal MI)
- All adults with type I diabetes

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.[22] 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 or

• 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.[9] 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).[23] Cholesterol lowering therapy is recommended in the following individuals:
• 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)
• 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 dm&d 14 September 2020. Costs do not take patient access schemes into consideration.

Additional information: budget impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues.

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

References

1. Daiichi Sankyo UK Ltd. Bempedoic acid film-coated tablets (Nilemdo®) Summary of product characteristics. European Medicines Agency www.ema.europa.eu. Last accessed [27 August 2020].
2. European Medicines Agency (EMA) European Public Assessment Report. Bempedoic acid (nilemdo®). 30/01/2020, EMA/CHMP/86202/2020. https://www.ema.europa.eu.
3. Ballantyne CM, Banach M, Mancini GBJ, Lepor NE, Hanselman JC, Zhao X*, et al.* Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study. Atherosclerosis. 2018;277:195-203.
4. Goldberg AC, Leiter LA, Stroes ESG, Baum SJ, Hanselman JC, Bloedon LT*, et al.* Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease: The CLEAR Wisdom Randomized Clinical Trial. JAMA.322(18):1780-8.
5. Laufs U, Banach M, Mancini GBJ, Gaudet D, Bloedon LT, Sterling LR*, et al.* Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. Journal of the American Heart Association. 2019;8(7).
6. Ray KK, Bays HE, Catapano AL, Lalwani ND, Bloedon LT, Sterling LR*, et al.* Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol. New England Journal of Medicine.380(11):1022-32.
7. ClinicalTrials.gov. A Multicenter Open-Label Extension (OLE) Study To Assess The Long-Term Safety and Efficacy of Bempedoic Acid (ETC-1002) 180mg. Available from: https://clinicaltrials.gov.
8. Banach M, Duell PB, Gotto AM, Jr., Laufs U, Leiter LA, Mancini GBJ*, et al.* Association of Bempedoic Acid Administration With Atherogenic Lipid Levels in Phase 3 Randomized Clinical Trials of Patients With Hypercholesterolemia. JAMA Cardiology. 2020;01:01.
9. Network SIG. SIGN 149. Risk estimation and the prevention of cardiovascular disease. 2017.
10. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical guideline [CG181]. National Institute for Health and Care Excellence, 2016.
11. ClinicalTrials.gov. A randomized, double-blind, placebo-controlled study to assess the effects of bempedoic acid (ETC-1002) on the occurrence of major cardiovascular events in patients with, or at high risk for, cardiovascular disease who are statin intolerant. Available from: https://clinicaltrials.gov.
12. Daiichi Sankyo Europe data on file. Delphi panel UK. 2019.
13. ABPI. Getting the best new treatments to patients faster than ever. Accelerated Access Collaborative ABPI Webinar
14. Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A*, et al.* A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technol Assess. 2007;11(14):1-160, iii-iv.
15. Cholesterol Treatment Trialists' Collaboration, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L*, et al.* Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet. 2015;385(9976):1397-405.
16. Koren MJ, Sabatine MS, Giugliano RP, Langslet G, Wiviott SD, Ruzza A*, et al.* Long-Term Efficacy and Safety of Evolocumab in Patients With Hypercholesterolemia. J Am Coll Cardiol. 2019;74(17):2132-46.
17. Smolina K, Wright FL, Rayner M, Goldacre MJ. Long-term survival and recurrence after acute myocardial infarction in England, 2004 to 2010. Circ Cardiovasc Qual Outcomes. 2012;5(4):532-40.
18. Wilson PW, D'Agostino R, Sr., Bhatt DL, Eagle K, Pencina MJ, Smith SC, et al. An international model to predict recurrent cardiovascular disease. Am J Med 2012; 125: 695-703 e1.

19. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13(5):509-18.
20. Luengo-Fernandez R, Gray AM, Bull L, Welch S, Cuthbertson F, Rothwell PM, *et al.* Quality of life after TIA and stroke: ten-year results of the Oxford Vascular Study. Neurology. 2013;81(18):1588-95.
21. Danese MD, Gleeson M, Kutikova L, Griffiths RI, Azough A, Khunti K, *et al.* Estimating the economic burden of cardiovascular events in patients receiving lipid-modifying therapy in the UK. BMJ Open. 2016;6(8):e011805.
22. National Institute for Health and Care Excellence. Identification and management of familial hypercholesterolaemia, 2008, udated 2019. Clinical Guideline 71.
23. JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart. 2014;100 Suppl 2:ii1-ii67.

This assessment is based on data submitted by the applicant company up to and including 30 October 2020.

**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.