NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Evinacumab for treating homozygous familial hypercholesterolaemia in people 12 years and over

1 Recommendations

1.1 Evinacumab alongside diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies is recommended, within its marketing authorisation, as an option for treating homozygous familial hypercholesterolaemia (HoFH) in people 12 years and over. It is only recommended if the company provides it according to the commercial arrangement (see section 2).

Why the committee made these recommendations

When LDL-C is not lowered enough by diet and LDL-C lowering therapies in people with HoFH, lipoprotein apheresis may be added. In adults, lomitapide may also be used but is not licensed for people aged 12 to 17 years.

Clinical trial evidence shows that evinacumab can lower LDL-C levels when statins and other lipid-lowering therapies have not reduced them enough. There is no data directly comparing evinacumab with lomitapide, and the results of an indirect treatment comparison are uncertain. There is also no long-term evidence on whether evinacumab reduces the risk of cardiovascular death or events such as heart attacks.

There are some uncertainties in the cost-effectiveness evidence comparing evinacumab with lomitapide in adults with HoFH. But, overall, there are cost savings with evinacumab compared with lomitapide. This means that, despite the

uncertainties in the evidence, evinacumab is a cost-effective use of NHS resources when compared with lomitapide in adults. The cost-effectiveness evidence in people aged 12 to 17 years is uncertain. Evinacumab costs more than LDL-C lowering therapies alone. But, because LDL-C lowering therapies have limited effectiveness in people with HoFH, there is a high unmet need in young people for effective treatments. So, evinacumab is recommended for the whole population for which it is licensed.

2 Information about evinacumab

Marketing authorisation indication

2.1 Evinacumab (Evkeeza, Ultragenyx) is indicated ‘as an adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and adolescent patients aged 12 years and older with homozygous familial hypercholesterolaemia (HoFH)'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for evinacumab.

Price

2.3 The list price of evinacumab is £6,433 per 345 mg vial for injection (excluding VAT; BNF online, accessed July 2024).

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes evinacumab available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Ultragenyx, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

Homozygous familial hypercholesterolaemia (HoFH)

The condition

3.1 HoFH is a rare genetic condition affecting the low-density lipoprotein receptor (LDLR). The clinical experts highlighted that it is rare because it needs the same gene alteration to be inherited from each parent. Mutations in genes affecting the functioning of LDLRs cause reduced uptake of low-density lipoprotein-cholesterol (LDL-C) into cells. This means LDL-C accumulates in the blood, leading to aortic valve disease in childhood and resultant early cardiovascular disease (CVD). This can be fatal if untreated. Early symptoms of HoFH include deposits of fat under the skin (known as xanthomas) and cholesterol deposits in the eye. The patient experts explained that HoFH can significantly affect quality of life because people with the condition must live with the symptoms of CVD from an early age. They added that people with HoFH and their carers worry about the risk of future cardiovascular events. The committee concluded that HoFH is a rare and debilitating condition with a large effect on quality of life.

Clinical management

Treatment options in adults

3.2 The clinical experts stated that the aim of treatment for HoFH is to lower LDL-C and that statins are the first treatment used. People may also have ezetimibe if the maximum tolerated dose of statin is not lowering LDL-C enough. If LDL-C levels stay higher than target LDL-C levels and the person has CVD, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors such as evolocumab or alirocumab can be offered. This combination is often referred to as lipid-lowering therapies (from now, LLTs). People whose LDL-C remains elevated on LLTs often have weekly lipoprotein apheresis to remove excess LDL-C from their blood. The patient experts explained that lipoprotein apheresis can be severely disruptive to people with HoFH because they need to take time off work or

school every week. Also, the benefits of lipoprotein apheresis are short lived after each administration. When apheresis is used for an extended period, a port or fistula for venous access usually needs to be created. This can be traumatic and painful. In adults whose LDL-C is higher than normal after all commonly used treatments have been tried, NHS England's Clinical Commissioning Policy on lomitapide for treating homozygous familial hypercholesterolaemia recommends lomitapide. The clinical experts explained that lomitapide is successful at lowering LDL-C levels in people with HoFH. But it can cause severe gastrointestinal side effects and needs adherence to a low-fat diet, which can be challenging to maintain. One patient expert stressed that even small increases in dietary fat caused nausea, diarrhoea, weakness, dehydration and a loss of appetite when they had lomitapide. The clinical experts highlighted that statins, ezetimibe and PSCK9 inhibitors have limited effectiveness in people with HoFH. This is because they target the LDL receptor, which is defective in HoFH. One clinical expert estimated that, in people with residual LDLR activity, LLTs only have around a 20% to 25% success rate in lowering LDL-C to target levels. So, the only treatments effective in controlling LDL-C in people with HoFH are lipoprotein apheresis and lomitapide. The committee concluded that a new treatment option for HoFH would be welcomed.

Treatment options in people aged 12 to 17 years

3.3 The committee noted that people with HoFH aged 12 years and over are included in the licence for evinacumab. The clinical experts highlighted that the current treatments for people aged 12 to 17 years (from now, young people) are unsatisfactory. This is because lomitapide only has a licence in adults, so young people can only have LLTs and lipoprotein apheresis. The committee recalled that LLTs are not effective at lowering LDL-C long term, and that apheresis can be traumatic and time consuming (see section 3.2). The clinical experts highlighted that LDL-C levels increase substantially in young people. So, treating HoFH as early

as possible may prevent LDL-C build up and reduce the risk of cardiovascular events. The clinical experts did not expect the effectiveness of evinacumab to differ in young people and adults, so healthcare professionals would want to use it as early as its licence allows. They explained that the population diagnosed with HoFH as young people is likely to be small because the homozygous form of the condition is so rare (see section 3.1). They estimated that there are only about 10 to 12 young people with HoFH in the UK. The committee considered whether this population is likely to increase with improved genetic testing. The clinical experts explained that genetic testing for HoFH is only offered if people are symptomatic or have a family history of CVD. The clinical experts advised that routine screening for HoFH is unlikely to be introduced soon, so the number of young people with HoFH is expected to remain small. The committee concluded that the number of young people with HoFH in the NHS is small, and there is a high unmet need for new treatments in this population.

Comparators in adults

3.4 The company considered lomitapide to be the only relevant comparator for evinacumab in adults. This was because evinacumab is expected to replace lomitapide in the pathway. The committee noted that the marketing authorisation for evinacumab specifies that it should be used as an adjunct to diet and LLTs, but it does not mention lomitapide. It agreed that this aligned with the company's positioning, so lomitapide and evinacumab would never be used together. The committee recalled that lomitapide is associated with toxicities and needs significant lifestyle changes (see section 3.2). It noted that the NHS commissioning policy for lomitapide estimates that, of the maximum 66 people with HoFH in the UK, 28% for whom lomitapide is an option do not have it. This is because they cannot or do not want to commit to the required low-fat diet or to avoid alcohol, or have comorbidities that increase the risk of liver toxicity. The committee noted that the NICE scope for evinacumab also included

LLTs (statins, ezetimibe, evolocumab) and lipoprotein apheresis as potential comparators. The clinical experts confirmed that these treatments would be used in people who cannot or do not want to have lomitapide. The committee next considered whether LLTs (with or without lipoprotein apheresis) would also be a comparator in people who can have lomitapide. It recalled that, unlike lomitapide, LLTs have limited effect in people with HoFH (see section 3.2). So, people who can and want to have lomitapide would not choose to have LLTs instead. This meant that LLTs (with or without lipoprotein apheresis) were not a comparator in this population. The committee concluded that the relevant comparator for evinacumab in adults was lomitapide. In adults that cannot or do not want to have lomitapide, continuing LLTs with or without lipoprotein apheresis was the relevant comparator.

Comparators in young people

3.5 The committee next considered the comparators for evinacumab in young people. It recalled that lomitapide only has a marketing authorisation in adults, whereas evinacumab is licensed in young people and adults (see section 3.3). So, the overall population eligible for evinacumab is likely to be larger than that for lomitapide. The clinical experts confirmed that LLTs with or without lipoprotein apheresis are the only options for young people with HoFH until they reach 18 years old and can have lomitapide. So, the committee concluded that continuing LLTs with or without lipoprotein apheresis was the relevant comparator in young people.

Clinical effectiveness

Clinical evidence for evinacumab

3.6 The main clinical trial evidence in the company submission came from the ELIPSE trial, a phase 3 randomised controlled trial. It included people with HoFH aged 12 years and over on stable doses of LLTs with an LDL-C level of 1.81 mmol/litre or over. In the double-blind treatment phase, people were randomised to 15 mg/kg of evinacumab (43 people) or

placebo (22 people), both administered intravenously every 4 weeks for 24 weeks. This was followed by an open-label treatment phase in which everyone in the trial had 15 mg/kg of evinacumab for a further 24 weeks. The company also submitted evidence for evinacumab from an open-label single-arm proof-of-concept study, R1500-CL-1331, and an open-label extension study, R1500-CL-1719. People from ELIPSE and R1500-CL-1331, and people who had never had evinacumab could all enter R1500-CL-1719. Results for R1500-CL-1719 are available for up to 120 weeks of follow up. The EAG highlighted that only 2 young people were enrolled in ELIPSE. So, the trial population may not have reflected the full population in which evinacumab would be offered in the NHS. The EAG noted that about 26% of the evinacumab arm in ELIPSE were also having lomitapide as a background treatment. It highlighted that this was not aligned with the company's positioning for evinacumab, which was as a replacement for lomitapide. The committee agreed that there were uncertainties about the generalisability of the ELIPSE results to the population with HoFH in the NHS. But it acknowledged the challenges of recruiting people to clinical trials in rare conditions (see section 3.1). It also noted that the dosing schedule in R1500-CL-1331 differed from the marketing authorisation for evinacumab. The committee concluded that ELIPSE and R1500-CL-1719 were the most appropriate data sources to inform the clinical effectiveness of evinacumab.

Key clinical trial results

3.7 The primary endpoint in ELIPSE was the percentage change in LDL-C from baseline to week 24. Compared with placebo, evinacumab was associated with a 49% reduction in mean LDL-C at week 24 (95% confidence interval [CI] -65% to -33%). Reductions in LDL-C continued up to week 48 in ELIPSE and week 120 in R1500-CL-1719 (exact results are academic in confidence and cannot be reported here). The committee noted that mortality and cardiovascular events were not collected in the clinical trials. This meant that a reduction in LDL-C had been used as a

surrogate endpoint for reducing mortality and cardiovascular events. The committee agreed that the link between LDL-C and cardiovascular mortality was uncertain. But it noted that using LDL-C as a surrogate endpoint had been accepted in previous NICE technology appraisals on treating primary hypercholesterolaemia or mixed dyslipidaemia, including NICE's technology appraisal guidance on inclisiran and on bempedoic acid with ezetimibe. The committee concluded that results from ELIPSE and R1500-CL-1719 suggest that evinacumab reduces LDL-C levels compared with placebo.

Indirect treatment comparison

3.8 Because ELIPSE only included a placebo comparator, the company did an unanchored matching-adjusted indirect treatment comparison (MAIC) to assess the efficacy of evinacumab compared with lomitapide. For lomitapide, the company used data from a single-arm study by Cuchel et al. (2013). This study included 23 people, who had lomitapide for a maximum of 56 weeks. The dosage of lomitapide was increased from 5 mg a day to 60 mg a day based on safety and tolerability. The median dosage was 40 mg of lomitapide a day. In the MAIC, 24-week data from ELIPSE was used for evinacumab and 26-week data from Cuchel et al. was used for lomitapide. The MAIC assessed the percentage change in LDL-C from baseline. The company adjusted the baseline characteristics from ELIPSE to match those from Cuchel et al. for known prognostic factors. These were age, history of coronary heart disease and LDL-C level. It also provided a scenario analysis that matched patient characteristics by age only. When matching all identified prognostic factors, the difference in mean LDL-C reduction from baseline for evinacumab was 15% greater than that for lomitapide (95% CI -37% to 7%). When matching for age alone, it was about 16% greater (95% CI -31% to -2%). The committee recalled that 26% of people in the evinacumab arm of ELIPSE had lomitapide as background therapy (see section 3.6). The EAG was concerned this could have biased the

comparison because some of the treatment effect in the evinacumab arm of ELIPSE may have resulted from concomitant lomitapide treatment. It preferred analyses provided by the company that excluded people who were having lomitapide with evinacumab. The committee noted that excluding these people substantially decreased the sample size in the analysis. Also, the results suggested that lomitapide was more effective than evinacumab at lowering LDL-C (mean LDL-C reduction from baseline was 6% higher for lomitapide, 95% CI -26% to 39%). The company highlighted that the ELIPSE subgroup analyses suggested that having lomitapide with evinacumab would not be more effective than having evinacumab alone. So, to exclude people who were having both evinacumab and lomitapide was unwarranted. The committee was concerned that the poor matching of baseline characteristics and small trial populations in the MAIC made the results extremely uncertain. It noted that none of the effect estimates reached statistical significance and that many of the confidence intervals passed 0. This suggested that it was plausible that there was no difference in clinical effectiveness between treatments. Because of this, the committee questioned whether any of the results from the MAIC were appropriate for decision making. The clinical experts explained that, although the treatments had similar effectiveness at the recommended dose, evinacumab had the potential to be more effective than lomitapide in clinical practice. This was because the toxicities associated with lomitapide mean that many people cannot tolerate higher doses. Adherence to lomitapide may also be worse because it is used orally every day, whereas evinacumab is an infusion administered every 4 weeks. The clinical experts considered that people in clinical practice are unlikely to have the LDL-C reduction seen in the trials. This was because many people having lomitapide in clinical practice have lower doses than the doses people in the clinical trials had. Based on this, the committee considered it plausible that evinacumab would be at least equally as effective as lomitapide in clinical practice. But it noted that the MAIC estimates that favoured evinacumab also included

lomitapide as a background therapy in the evinacumab arm of ELIPSE. The committee agreed that this introduced substantial uncertainty into the results. It recalled that the company expected evinacumab to replace lomitapide, so the 2 treatments would not be used together in clinical practice. The committee concluded that, although it is plausible that evinacumab will work at least equally as well as lomitapide in clinical practice, the true difference in treatment effect was unknown. It preferred the treatment effect from the MAIC that excluded people having lomitapide in the evinacumab arm of ELIPSE. This was to minimise the uncertainty in the results and because the people in this analysis aligned with the people in the company's decision problem.

Adverse events

3.9 During the 24 weeks of randomised treatment in ELIPSE, about 66% (29 people) having evinacumab had an adverse event compared with 81% (17 people) having placebo. Of these, about 11% (5 people) in the evinacumab arm had a treatment-related adverse event, with injection site reactions and inflammation of the nasal passage most commonly reported. Only about 5% (1 person) of the placebo arm had a treatment-related adverse event. The committee recalled that there was no safety data with which to compare evinacumab and lomitapide directly (see section 3.8). But it recalled that lomitapide was associated with gastrointestinal side effects that could be severe and dose-limiting (see section 3.2). The clinical experts explained that they expected an improved side-effects profile with evinacumab compared with lomitapide. The committee considered this in its decision making.

Economic model

Company's modelling approach

3.10 To assess the cost effectiveness of evinacumab, the company developed a Markov model based on cardiovascular events. The company assumed that people entered the model in a stable HoFH health state, then

transitioned to 1 of 5 acute non-fatal cardiovascular events (stable angina, unstable angina, myocardial infarctions, transient ischaemic attack or stroke). They remained in the acute event state for a year. They then transitioned to the post-event state or had another acute event. Acute- and post-event health states were associated with different costs and utility benefits. People could transition to cardiovascular- and non-cardiovascular-related death from any health state. People were assumed to have background LLTs and lipoprotein apheresis at the rates used in ELIPSE. These rates were applied equally to both the intervention and comparator arms. The committee agreed that the company's general model structure was appropriate for decision making.

Population in the model

3.11 People with HoFH entered the company's model aged 42 years. This was based on the average age in the ELIPSE trial at baseline. The committee recalled that people aged 12 years and over are included in the licence for evinacumab and that there is a high unmet need in young people (see section 3.2 and section 3.3). The committee noted that the company had not presented cost-effectiveness analyses for young people entering the model aged 12 years. This was because there was a lack of clinical data in this population (only 2 people in ELIPSE had been under 18; see section 3.6). So, the data in the model was from adults only and may not have been generalisable to young people. The EAG highlighted that the lack of data in young people made the clinical effectiveness of evinacumab extremely uncertain. But the committee was concerned that the benefits of starting evinacumab early on long-term cardiovascular outcomes may not have been captured in the company's or EAG's base cases. It noted that the EAG had provided scenario analyses that assumed people started evinacumab aged 12 years. The committee was concerned that some of the model inputs in the EAG's scenarios, such as the cardiovascular event and mortality rates, were based on much older populations. So, it would have been inappropriate to extrapolate this data

to young people. The committee noted that there were few young people with HoFH in the NHS (see section 3.3). But it agreed that the full impact of evinacumab in these people was not captured in the company's and EAG's base cases. It concluded that the EAG's cost-effectiveness analyses with a model starting age of 12 years were not appropriate for decision making because of the high uncertainty in the estimates.

Baseline cardiovascular event history

3.12 The company assumed that no one had prior cardiovascular events when they entered the model. The EAG was concerned that the company's approach did not capture the difference in outcomes between people having a first cardiovascular event (primary prevention population) and subsequent cardiovascular events (secondary prevention population). The committee recalled that people entered the model aged 42 years. The clinical experts explained that it was unusual for people with HoFH to reach this age without having had a cardiovascular event. They quoted trial data in which 9 of 11 people over 42 years (80%) had already had at least 1 cardiovascular event. This aligned reasonably well with the EAG's base case in which 70% of people were modelled as the secondary prevention population. These people were distributed to post-event health states when they entered the model, and these health states had worse baseline utilities than the primary prevention population. The committee agreed it was appropriate to model primary and secondary prevention populations separately. It concluded that the assumption in which 70% of people had at least 1 prior cardiovascular event at baseline best aligned with the population in clinical practice.

Baseline LDL-C

3.13 The committee recalled that the company used change in LDL-C as a surrogate endpoint for predicting cardiovascular events (see section 3.6). The company did not use the baseline LDL-C from ELIPSE in its base-case model. Instead, it used the baseline LDL-C from Thompson et al.

(2018), which provided the modelled cardiovascular mortality data (see section 3.14). It did this to capture the relationship between LDL-C and cardiovascular mortality. The company noted differences in background LLT use between Thompson et al. and ELIPSE. To account for this, it adjusted the baseline LDL-C value from Thomspon et al. by the difference in LLT use between studies. It also applied a treatment effect for each LLT (using sources from the literature). This approach resulted in a baseline LDL-C of 7.93 mmol/litre. The EAG was concerned about the company's approach. It stated that adding the treatment effect of each LLT individually increased the uncertainty in the overall estimate. It noted that both the baseline LDL-C and the reduction in LDL-C in people whose condition responded to evinacumab was lower in ELIPSE than in the company's model. It was also concerned that some of the efficacy estimates for LLTs had come from the company's MAIC, which it considered to be highly uncertain (see section 3.8). The EAG considered that ELIPSE best represented current NHS care, so used the ELIPSE baseline LDL-C in its model. But, to align with the source of cardiovascular mortality data, it calculated the difference in baseline LDL-C from ELIPSE and Thompson et al. (a difference of 2.1 mmol/l). It then used this value to represent the change in LDL-C after treatment with background LLTs. The committee agreed that the company's approach introduced unnecessary complexity into the baseline LDL-C calculation. It preferred the EAG's approach to modelling baseline LDL-C for decision making.

Cardiovascular mortality

3.14 ELIPSE did not capture mortality, so the company used the study by Thompson et al. (2018) to inform cardiovascular death rates. It applied parametric curves to the mortality data from Thomspon et al. to extrapolate long-term mortality in people with HoFH. The company chose the Gompertz curve for its base case because it had the best fit, both statistically and visually, to the observed data from Thomspon et al. The

EAG highlighted that the company's approach may have overestimated death rates in people with HoFH. This was because treatment at the end of the study by Thompson et al. was better than at the start of the study. In particular, people alive at the end of the study had access to statins earlier and used them for longer than people who died during the study. People alive at the end of the study also had more frequent and effective lipoprotein apheresis. The EAG acknowledged that using cardiovascular mortality rates from people with HoFH was preferable to using those from the general population. But it was concerned that the people whose treatments were most similar to current NHS practice in Thomspon et al. were the people alive at the end of the study. So, a mortality rate could not be estimated from these people. The EAG provided a scenario in which mortality rates were extrapolated using the Weibull curve, which had the second best fit and resulted in lower mortality risks. The committee agreed that there was large uncertainty in the long-term mortality predictions. But it noted that both the EAG and company had used the Gompertz extrapolation in their base cases. The committee concluded that, although uncertain, the Gompertz parametric curve was appropriate to extrapolate cardiovascular mortality because it best fit the limited data available.

Real-world dose of lomitapide

3.15 In January 2024, after release of the final draft guidance for the appeal period, NICE received a non-appeal request for a change to the guidance. A commentator identified that the dose of lomitapide used in the economic modelling for evinacumab was incorrect. It shared some data from d'Erasmo et al. (2022) and some commercial-in-confidence data. This showed that a lower dose of lomitapide is used in clinical practice than in the company's base case. For the first committee meeting, the company, EAG and committee agreed that the median lomitapide dosage of 40 mg per day from Cuchel et al. (2013) was suitable for decision making. This is equivalent to 2.2 capsules per day when weighted by the number of

people having a different number of capsules. Lomitapide has the same cost per capsule regardless of dose (5, 10 and 20 mg capsules of lomitapide are available in the NHS). So, the number (not dose) of lomitapide capsules was the important input for costing purposes. If the lomitapide capsule number was too high in the economic analysis of evinacumab, the costs of lomitapide were potentially overestimated. This raised uncertainty about the cost effectiveness of evinacumab. NICE withdrew the final draft guidance for this evaluation. It then held a stakeholder engagement requesting further information from all stakeholders about the dose, capsule number and efficacy of lomitapide for the treatment of HoFH in NHS practice. Responses were received from NHS England, Ultragenyx (marketing authorisation holder for evinacumab), Chiesi (marketing authorisation holder for lomitapide), HEART UK, and a clinical expert. Stakeholder responses were discussed at a second committee meeting in July 2024. NHS England shared real-world lomitapide dosing data from 18 people with HoFH from 5 NHS trusts in England. The average daily dose of lomitapide was 16.9 mg, with a range of 5 to 30 mg. The EAG assumed the number of capsules per dose and estimated an average of 1.4 lomitapide capsules per day from the NHS England data. HEART UK also shared real-world dosing data from people with HoFH in England. It reported that all people are on between 1 or 2 lomitapide capsules a day, with an average of 1.7 capsules. Chiesi shared data on the dose of lomitapide used in clinical practice. This included 11 global studies and commercial-in-confidence data from patients with HoFH in England. Chiesi highlighted that the studies showed that a lower dose of lomitapide is used in clinical practice than in the company's base case. In response to the stakeholder engagement, Ultragenyx explained that the dose of lomitapide changes depending on response and tolerability. It added that dosing data from Cuchel et al. was the only evidence available on lomitapide's efficacy from a phase 3 study. Ultragenyx considered that the observational studies identified by Chiesi should not be used in modelling. It argued that if data from observational

studies is used, it should be as part of a cost-minimisation analysis. At the second committee meeting, the clinical experts highlighted that the data shared by HEART UK was accurate and reflected their clinical experience of lomitapide. They added that people typically have 20 mg of lomitapide a day, with less than half of people tolerating more than this. They also noted that the HEART UK data was collected in England, but Cuchel et al. was based on European data. One patient expert explained that people on a lower dose of lomitapide would have increased background treatments such as LDL apheresis to compensate for reduced lomitapide efficacy. This means that the cost of lower doses of lomitapide may actually be higher than modelled. The EAG noted that the new evidence submitted during the stakeholder engagement made clear that the 2.2 capsules assumed for its base case for the first committee meeting was too high. It preferred to use the 1.7 capsules reported by HEART UK. This was because this value is based on actual capsule usage and not assumed capsule usage derived from lomitapide doses in the NHS England data. The committee concluded that 1.7 capsules of lomitapide a day should be used in modelling because the figure is based on actual capsule usage in England.

Relative treatment effect of lomitapide

3.16 After concluding on the appropriate number of lomitapide capsules to use in economic modelling (see section 3.15), the committee considered any impact on the associated treatment effectiveness of lomitapide. It recalled its previous conclusions on the uncertainties around the relative treatment effect of evinacumab and lomitapide (see section 3.8). Chiesi commented that the new evidence it shared shows that lomitapide is highly effective at lower doses. HEART UK commented that the associated efficacy of lomitapide is not necessarily dose dependent because lomitapide leads to an LDL C reduction of between 30% and 70%. The EAG considered that there was no robust data to inform a reliable estimate of the treatment effect of lomitapide alone or compared with evinacumab for the real-world

doses used in NHS clinical practice. It explained that the main driver of the cost-effectiveness results was cost based. It suggested a cost-minimisation analysis that assumed equal clinical effectiveness for evinacumab and lomitapide. This was because the incremental quality-adjusted life years (QALYs) for evinacumab compared with lomitapide were very small. The committee concluded that a cost-minimisation analysis was appropriate when considering changes to the modelled number of daily lomitapide capsules.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.17 For the first committee meeting, the company's base case compared evinacumab with lomitapide (both with background LLTs and lipoprotein apheresis). The lomitapide arm had 2.2 capsules of lomitapide per day and included the full MAIC population. This resulted in an incremental cost-effectiveness ratio (ICER) in which evinacumab was dominant (that is, it had lower costs and higher QALYs than lomitapide). This was when considering confidential discounts for evinacumab and comparators (exact ICERs are confidential and cannot be reported here). The EAG's preferred base case at the first committee meeting used the treatment effect from the MAIC excluding people who had lomitapide in the evinacumab arm of ELIPSE (and assumed 2.2 capsules of lomitapide per day for the lomitapide arm). This resulted in slightly lower QALYs but also lower costs than lomitapide. The EAG also presented a base case comparing evinacumab with LLTs (with and without lipoprotein apheresis). In this base case, the ICER was over £30,000 per QALY gained. For the second committee meeting, the company offered a revised patient access scheme for evinacumab. The EAG shared an updated base case that assumed:

- a dosage of 1.7 capsules of lomitapide daily (see section 3.15)

- equal efficacy for evinacumab and lomitapide via a cost-minimisation analysis (see section 3.16).

In this updated base case, evinacumab was cost saving compared with lomitapide.

Committee's preferred ICER compared with lomitapide

3.18 The committee noted that its preferred assumptions for comparing evinacumab with lomitapide aligned with the EAG's base case presented at the second committee meeting. It recalled the uncertainty in the treatment effect of lomitapide compared with evinacumab (see section 3.8). The committee also recalled its conclusion at the second committee meeting that a cost-minimisation analysis was appropriate because of this uncertainty and the very small incremental QALYs (see section 3.16). It noted that evinacumab was cost saving compared with lomitapide when using the EAG's cost-minimisation analysis that assumed an equal treatment effect. So, the committee considered that evinacumab was cost effective compared with lomitapide.

Committee's preferred ICER compared with LLTs

3.19 The committee next considered the comparison with LLTs (with and without lipoprotein apheresis) provided by the EAG. It noted that these ICERs were above £30,000 per QALY gained. It recalled that the population having LLTs included young people, but the starting age in the EAG's base case was 42 years. So, the full benefits of treating young people may not have been captured (see section 3.11). Because of this, it considered that the ICERs in the EAG's base case for evinacumab compared with LLTs were highly uncertain. The committee recalled that the EAG had provided scenarios in which people entered the model aged 12 years to represent the full population in the marketing authorisation for evinacumab. It noted that the EAG's scenarios had ICERs above £30,000 per QALY gained, but recalled its conclusion that they were not fit for

decision making. This was because the scenarios were informed by data from a much older population (see section 3.11). The committee considered that there were no reliable cost-effectiveness analyses with LLTs on which to base its decision. But it recalled that there is an unmet need in this population. This is because LLTs have limited effect in people with HoFH, and lipoprotein apheresis can be traumatic and time consuming (see section 3.2 and section 3.3). It also considered that a negative recommendation in people currently having LLTs may create an inequality of access based on age because this population includes young people (see section 3.20). The committee considered these factors exceptional and agreed that they warranted flexibility in its recommendation. So, it recommended evinacumab for the whole population in its marketing authorisation.

Other factors

Innovation

3.20 The committee considered whether evinacumab was innovative. It noted that evinacumab is a first-in-class medicine with a novel mechanism of action. Unlike LLTs, it works independently of the LDLR, meaning that people with a complete absence of LDLR function could still benefit from treatment. Also, it noted that evinacumab addresses an unmet need for new treatments to lower LDL-C, especially in people having LLTs who have unsatisfactory treatment options (see section 3.2 and section 3.3). The committee recalled that treating young people may result in long-term benefits from controlling LDL-C levels and reducing the risk of cardiovascular events. It agreed that these benefits were not fully captured in its preferred model, which had a starting age of 42 years (see section 3.11). The committee also acknowledged that evinacumab may improve adherence to treatment because it is administered every 4 weeks as an infusion. The committee concluded that evinacumab is innovative

and some benefits were not included in the modelling. It considered this in its decision making.

Equality

3.21 Several potential equality issues were raised during the evaluation. The committee recalled that the marketing authorisation for evinacumab included young people having LLTs in clinical practice (see section 3.3). The committee noted that the ICERs for evinacumab compared with LLTs were above £30,000 per QALY gained in young people. But it added that a negative recommendation in this population may create an inequality of access based on age. The committee noted the outcome of the appeal for NICE's technology appraisal guidance on molnupiravir, remdesivir and tixagevimab plus cilgavimab for treating COVID-19. In this, the appeal panel considered that children with severe COVID-19 would be at a particular disadvantage because, unlike adults, they cannot access any other licensed treatments. The appeal panel agreed that excluding children from the recommendation was not a proportionate means of achieving NICE's legitimate aim when:

- taking account of the rarity of COVID-19 in children, and
- consequently, the minimal burden that a positive recommendation for remdesivir may have on overall NHS resource utilisation.

So, the appeal panel considered the exclusion of children an indirect discrimination, even if the technologies were not cost effective in this population. The committee agreed that the appeal panel's principles applied to this evaluation of evinacumab. It considered that it could apply flexibility as part of the principles that guide the development of NICE guidance and standards. These emphasise the importance of considering the distribution of health resources fairly within society as a whole, and factors other than relative costs and benefits alone. The committee concluded that, on balance, a negative recommendation in

young people could be discriminatory. Also, it concluded that, given the small number of young people with HoFH (see section 3.3), it would not be proportionate in achieving the committee's aims. The committee recalled that this potential inequality had been an important factor in its decision to recommend evinacumab for the full population in its marketing authorisation (see section 3.18). So, any inequality of access by age had been addressed. The committee next considered whether there were any other potential equalities issues for evinacumab. It noted that the treatments provided could vary across the NHS depending on region and availability of specialist care. The clinical experts explained that evinacumab will initially be administered in a hospital but has the potential to be administered at home. The committee concluded that its recommendation would not affect people protected by the equality legislation any differently.

Conclusion

Recommendation

3.22 The committee acknowledged that there were negative QALYs accrued in its preferred MAIC analyses of evinacumab compared with lomitapide. But it concluded that the results of the MAIC were uncertain and the QALY differences were very small. So, it agreed to assess the cost effectiveness of evinacumab using a cost-minimisation analysis with lomitapide. It also agreed that evinacumab was an alternative option to lomitapide, so the 2 should not be used together. The results showed that evinacumab was cost saving compared with lomitapide. The cost-effectiveness analyses compared with LLTs were above the threshold normally considered a cost-effective use of NHS resources. But the committee considered these estimates were not appropriate for decision making. It acknowledged that the population who have LLTs (with or without lipoprotein apheresis) have a high unmet need because:

- LLTs have limited effectiveness in people with HoFH

- lipoprotein apheresis can be traumatic and time consuming
- this population includes young people, so there is a potential for an inequality of access by age.

The committee considered these exceptional circumstances that warranted flexibility in its recommendation. So, it recommended evinacumab for the whole population in its marketing authorisation.

4 Implementation

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

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

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has HoFH and the healthcare professional responsible for their care thinks that evinacumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

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

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

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

Chair

Stephen O'Brien

Chair, technology appraisal committee C

NICE project team

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

Owen Swales, Emma Douch

Technical leads

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