NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Evaluation consultation document

Odevixibat for treating progressive familial intrahepatic cholestasis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using odevixibat in the context of national commissioning by NHS England. The highly specialised technologies evaluation committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

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

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

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of odevixibat in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: September 2021

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

After consultation:

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

For further details, see the interim process and methods of the highly specialised technologies programme.

The key dates for this evaluation are:

Closing date for comments: 7th October 2021

Second evaluation committee meeting: 10th November 2021

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

1 Recommendations

1.1 Odevixibat is not recommended, within its marketing authorisation, for treating progressive familial intrahepatic cholestasis (PFIC) in people 6 months and older.

1.2 This recommendation is not intended to affect treatment with odevixibat that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children and young people, this decision should be made jointly by them, their clinician, and their parents or carers.

Why the committee made these recommendations

PFIC is a rare and serious genetic condition that reduces or stops the flow of bile acids from the liver. This can cause severe itching (pruritus), poor growth and liver damage. PFIC severely affects the quality of life of people with the condition, and of their families and carers. It is fatal if untreated. Current treatment includes medicines not licensed for this condition (off label), then surgery such as an operation called partial external biliary diversion (PEBD) and, finally, a liver transplant.

Results from clinical trials suggest that, in people with the PFIC types 1 and 2, odevixibat reduces bile acid levels in the blood and pruritus compared with placebo (with or without off-label medicines). There is limited data for other types of PFIC. Also, there is no evidence that uses the dose escalation schedule that would be used in NHS practice, or that compares odevixibat with PEBD. So, the effectiveness of odevixibat in clinical practice is uncertain.

The cost-effectiveness estimates are all much higher than what NICE normally considers an acceptable use of NHS resources within the context of a highly specialised service. So, odevixibat is not recommended.

2 The condition

2.1 Progressive familial intrahepatic cholestasis (PFIC) is the name given to a group of genetic disorders that affect the liver. They result in the flow of bile from the liver to the gastrointestinal tract being reduced or stopping completely. This causes an accumulation of bile in the liver cells (cholestasis), which start to die and are replaced with scar tissue. This leads to cirrhosis (severe scarring) and liver failure. PFIC is caused by mutations in the genes that encode the proteins involved in transporting bile out of the liver, adversely affecting their function. Three main types have been identified. The most prevalent, PFIC2, is caused by mutations in the ABCB11 gene. PFIC1 is caused by mutations in the ATP8B1 gene and PFIC3 by mutations in the ABCB4 gene. Rarer types, such as PFIC4, PFIC5 and PFIC6, have been identified. PFIC is typically inherited in an autosomal recessive pattern, meaning that 2 copies of the mutated gene (1 from each parent) must be present for it to develop. In PFIC1 and PFIC2, symptoms usually occur in the first months of life. PFIC3 can also appear later in infancy, in childhood or even during young adulthood. PFIC progresses at varying rates dependant on the type, but usually develops into cirrhosis within the first decade of life. It is fatal if untreated.

2.2 People with PFIC have a wide range of symptoms, determined primarily by the type they have. However, in all types, the condition is characterised by severe pruritus (itching), jaundice and raised serum bile acid levels. Diagnosis is primarily clinical. Other symptoms occurring outside the liver include diarrhoea, fat-soluble vitamin deficiencies and poor growth. These are more common in PFIC1. PFIC2 in particular is characterised by more rapid disease progression and a higher risk of liver cancer.

2.3 The prevalence of PFIC in England is unknown. However, worldwide estimates range between 1 per 50,000 to 1 per 100,000 live births. The marketing authorisation for odevixibat covers all types of PFIC.

2.4 There are no licensed medicines for PFIC. Initial management includes off-label medicines (for example, ursodeoxycholic acid, rifampicin, cholestyramine). The aim with these is to control the cholestatic pruritus. They are often given in combination and used alongside nutritional management, such as vitamin supplements to optimise nutrient absorption and promote growth. Surgical options are used when pruritus persists despite these off-label medicines. It includes surgical biliary diversion (SBD) and liver transplant. Partial external biliary diversion is the most common form of SBD and involves diverting bile away from the gallbladder via an external stoma. Liver transplant is needed by most people with PFIC.

3 The technology

3.1 Odevixibat (Bylvay, Albireo Pharma) is a selective inhibitor of the ileal bile acid transporter (IBAT). IBAT is involved in the absorption of bile acids in the small intestine for circulation back to the liver. Odevixibat stops the recycling of bile acids, increasing their excretion through the colon and lowering hepatic and serum bile acid levels. It has a marketing authorisation under 'exceptional circumstances' for 'the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older'.

3.2 Odevixibat is administered daily as a capsule or sprinkled on food. The starting dose is 40 micrograms/kg/day up to a maximum dose of 222 micrograms/day based on a weight of 55.5 kg. After 3 months of continuous therapy, the dose may be escalated to 120 micrograms/kg/day if there has not been an adequate clinical response.

3.3 The adverse reactions listed in the summary of product characteristics for odevixibat include: diarrhoea, abdominal pain, soft stools and hepatomegaly (an enlarged liver). For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.4 Odevixibat is available as a pack of 30 capsules. The cost per pack of 200 microgram capsules is £2,620, per pack of 400 microgram capsules is £5,240, per pack of 600 microgram capsules is £7,860 and per pack of 1,200 microgram capsules is £15,720 (excluding VAT; company's evidence submission) The company has a commercial arrangement, which would apply if the technology had been recommended.

4 Consideration of the evidence

The evaluation committee (see section 6) considered evidence submitted by Albireo pharmaceuticals, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). See the committee papers for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

4.1 Progressive familial intrahepatic cholestasis (PFIC) is a life-threatening condition. The patient experts highlighted that the complications of PFIC are multifaceted and significantly affect a child's development. The clinical experts stressed that, when PFIC is untreated, there is gradual loss of liver function, associated with pruritus and poor growth, which can be severe. The rate of progression can be rapid, especially for people with PFIC2. For this type, symptoms occur in newborns, and it often progresses to end-stage liver disease within the first few years of life. The clinical and patient experts stated that malnutrition, a lack of fat-soluble vitamins and the high bilirubin levels associated with cirrhosis can also affect neurological function. The committee concluded that PFIC is a complex and progressive condition, and that there are variations in symptoms and severity depending on the type.

Impact of the condition on people with PFIC and their families

4.2 The patient experts explained that the quality of life of a child with PFIC may be extremely poor. They emphasised that the pruritus can be debilitating, and that people can scratch themselves to the point of bleeding and skin damage. The patient experts stressed the profound nature of the itching, describing it as “itching from the inside out”. Poor growth is a common concern for carers, particularly in PFIC1. The clinical experts explained that children with PFIC eat a specific diet and take fat-soluble vitamin supplements to improve nutrient absorption. One patient expert highlighted that children may need a feeding tube to help manage the condition, which can be traumatic for the children as well as challenging for carers. Children with PFIC often have their education severely disrupted. This can be because of absence through illness and hospital attendances, and disrupted sleep impairing their ability to learn when at school. When compounded by condition-related learning disabilities, the educational attainment and social development of children with PFIC may be significantly affected. Carers explained that they needed to provide constant care to children with PFIC. Commonly, the demands are such that carers cannot work full time, resulting in loss of earnings and implications for career development. One carer explained that she could no longer carry on with her job as her daughter deteriorated because of the demands of juggling hospital visits and sleepless nights. The patient experts stressed that a diagnosis of PFIC affects the entire family. Siblings can be affected by the large number of hospital visits, sleepless nights and experience of seeing a sibling suffer. The unpredictability of the condition, particularly the speed of progression, can cause anxiety and other psychological difficulties for people with PFIC and their families. The committee concluded that PFIC has a significant effect on the quality of life of people with the condition, family members and carers.

Current management

4.3 The committee noted that there are no medicines licensed for PFIC in the UK. With medicines used off label, such as ursodeoxycholic acid, cholestyramine and rifampicin, the aim is to control the pruritus and delay progression to a liver transplant. However, response to off-label medicines varies, and there are no data from randomised controlled trials to support their clinical effectiveness. The clinical experts explained that cholestyramine is only commonly used in newborns because older children find it hard to tolerate. Surgical options such as partial external biliary diversion (PEBD) are associated with a decrease in serum bile acid levels and increased native liver survival. However, the clinical experts explained that PEBD is rarely used in the NHS and is only an option in a limited group, for example, those who have no liver fibrosis and whose liver disease is not advanced. The committee heard that, for PEBD, an external stoma needs to be created. This can be distressing and can have a significant effect on quality of life. There are also risks of complications such as electrolyte disturbance, dehydration and problems with the stoma. More recently adopted methods of surgical biliary diversion (SBD), such as an internal biliary drainage or internal ileal exclusion avoid the need for an external stoma bag. But, there is a lack of data about their relative benefit. The clinical experts explained that these methods are generally used as a longer-term solution in people whose condition has responded to PEBD but do not want or cannot tolerate an external stoma bag. For people who do not have SBD, or when pruritus persists despite surgery, liver transplant is the only remaining option.

4.4 The committee heard that a liver transplant is needed for most people with PFIC by age 20 years. This is because of liver disease and uncontrollable pruritus. The patient experts explained that liver transplant can be successful in resolving pruritus, so significantly improving the quality of life for children with PFIC and their carers. However, transplants are associated with complications such as infection, increased risk of skin or

liver cancer and life-threatening complications of graft rejection. Life-long immunosuppression, frequent hospital visits and regular monitoring for rejection after transplants are big concerns for people with PFIC and their families, as is the potential for recurrence of pruritus. The committee recognised that treatment options for PFIC are currently limited. It concluded that there was an unmet need for a new treatment for this condition.

4.5 The clinical experts explained that the current pathway of care for people with PFIC varies depending on the type. They explained that control of pruritus with off-label medicines such as ursodeoxycholic acid is more successful in people with PFIC3 than with PFIC1 and PFIC2. This means that people with PFIC3 are less likely to progress to surgery. They clarified that PEBD is most effective at reducing serum bile acid levels in PFIC2. However, long-term outcomes after the procedure, such as time to transplant, are uncertain because of a lack of data. The clinical experts highlighted that liver transplant is less likely to be offered to people with PFIC1. This is because of the potential for lasting non-liver complications including severe diarrhoea and pancreatitis and the high risk of recurrent pruritus. The committee concluded that the current pathway of care for PFIC is largely determined by type.

4.6 The company has positioned odevixibat as a first-line treatment for PFIC. Because no active treatment is routinely commissioned in the NHS for PFIC, the committee agreed that standard care without odevixibat was the appropriate comparator, as listed in the NICE scope. The company considered this included SBD such as PEBD but did not include off-label medicines. This was because people having odevixibat could also have off-label medicines for symptom management and that these medicines have poor clinical effectiveness. The ERG noted that off-label medicines were included in the NICE scope and would form part of standard care without odevixibat. It also stated that odevixibat had the potential to be

used before or after PEBD. The clinical experts highlighted that, if odevixibat was approved, off-label medicines would be started in the time leading up to diagnosis being confirmed. They also pointed out that off-label medicines would be started in babies younger than 6 months, who are not included in the marketing authorisation for odevixibat. The clinical experts confirmed that odevixibat would most likely be started in people having off-label medicines who had little or no drop in serum bile acid levels. They also thought that odevixibat could plausibly replace surgical options such as PEBD. However, the committee heard that pruritus in PFIC is complex and multifactorial. This means that people whose condition does not respond to odevixibat might also be offered PEBD, especially given the long waiting list for a liver and the low use of transplant for PFIC1. The clinical experts highlighted that odevixibat would not be used in people with PFIC2 who had a BSEP3 mutation, which results in a complete absence of the bile salt export pump protein. The committee concluded that the comparators for odevixibat in this appraisal were off-label medicines and SBD, including PEBD, but that sequential use of odevixibat and PEBD was possible.

4.7 The patient and clinical experts highlighted that there is an unmet need for treatments specifically targeting PFIC. They emphasised that odevixibat has the potential to improve quality of life, remove the need for SBD and delay the time to transplant for people with PFIC. The committee heard that complete relief of pruritus would represent a successful treatment, but anything to reduce itching would be beneficial. The clinical experts noted the need for a treatment that, in addition, both improved growth and preserved liver function. The committee recalled that cholestyramine is effective at lowering serum bile acid levels, but that it can be poorly tolerated (see section 4.3). It concluded that people with PFIC and their families would welcome odevixibat as a treatment for the condition.

Impact of the new technology

Clinical trial evidence

4.8 The main clinical trial evidence for odevixibat came from a phase 3 completed randomised controlled trial, PEDFIC1, and an ongoing single-arm open-label extension study, PEDFIC2. These trials enrolled people with a clinical diagnosis of PFIC1 or PFIC2 who had elevated serum bile acid levels and cholestatic pruritus:

- PEDFIC1 enrolled children 6 months and older, 23 of whom had odevixibat 40 micrograms/kg/day and 19 of whom had 120 micrograms/kg/day. A further 20 people had placebo. The follow-up period was 24 weeks.
- PEDFIC2 is an ongoing long-term follow-up study of PEDFIC1. It has enrolled 71 people who have had odevixibat 120 micrograms/kg/day. This includes 53 people in cohort 1 who had previously participated in PEDFIC1 (19 who had 40 micrograms/kg/day, 15 who had 120 micrograms/kg/day and 19 who had placebo) and 16 people in cohort 2. Cohort 2 includes people of any age who weighed over 5 kilograms with any type of PFIC who either had not met the eligibility criteria for PEDFIC1 or were eligible for enrolment after PEDFIC1 recruitment had been completed, so had not had odevixibat before. Interim data from week 24 analyses were available from a July 2020 data cut.

The company also provided evidence for odevixibat from a completed exploratory phase 2 study. This study enrolled 20 children with cholestatic pruritus of any cause, who were allocated to odevixibat at doses of 10, 30, 60, 100 or 200 micrograms/kg/day for 4 weeks. The committee noted the wide range of odevixibat doses and that only 10 people in the trial had PFIC (types 1, 2 or 3). The committee concluded

that the PEDFIC1 and PEDFIC2 studies were the most appropriate data sources for odevixibat.

Comparator clinical-effectiveness evidence

4.9 The committee first considered the clinical-effectiveness evidence for odevixibat compared with off-label medicines. It noted that most people in both the odevixibat and placebo arms of PEDFIC1 were having concurrent off-label medicines. For this reason, it agreed that PEDFIC1 provided relevant comparative data, as off-label medications form part of the current standard care and are likely to be given alongside odevixibat in clinical practice. The company did not present any data comparing odevixibat with PEBD or other types of SBD. It explained that an indirect comparison is planned that will compare odevixibat with standard care both with and without SBD. Comparative clinical-effectiveness data in the company's model came from NAPPED. This was a natural history cohort study that included 130 people with PFIC1 and 264 people with PFIC2 having standard care. The median follow-up time was 4.1 years (range 1.5 to 12.3 years). During this time, 48% of people with PFIC1 and 23% with PFIC2 had SBD. The committee agreed no evidence had been presented to compare odevixibat with PEBD. It concluded that the most appropriate comparative data source available for off-label medications was PEDFIC1.

Clinical trial outcomes

4.10 The primary outcome for PEDFIC1 for Europe and the rest of the world (RoW) was the proportion of patients who had a reduction of at least 70% in the serum bile acid level from baseline or levels that reached 70 micromol/litre or less. The primary outcome for PEDFIC2 (Europe and RoW) was the change in serum bile acid levels from baseline over the treatment period. The primary outcome in the US for both PEDFIC1 and PEDFIC2 was the proportion of positive pruritus assessments over the treatment period. The company measured this using a new observer-

reported outcomes instrument (ObsRO) developed for this purpose. The ObsRO instrument captures scratching on a scale of 0 (representing no scratching) to 4 (representing the worst possible scratching) using twice-daily patient and carer questionnaires. A positive pruritus response is defined by the company as an observer-reported scratching score of 1 or below, or a reduction of 1 or more points from baseline. Both studies also collected data on changes in growth, liver function, health-related quality of life, and the number of people having surgery or liver transplants. The patient experts explained that a reduction in pruritus would have the biggest effect on the quality of life of people with PFIC. The clinical experts explained that the relationship between serum bile acid levels and pruritus levels is complex, and that the 2 do not always correlate. Nonetheless, in general, lower serum bile acid levels are associated with improved pruritus and native liver survival. The patient experts highlighted that improvements in growth and liver function tests are important outcomes to people with PFIC. This is because they are generally associated with reduced pruritus, and improved sleep and quality of life. The committee concluded that the main outcomes important to clinicians and people with PFIC and their families were captured in the company's clinical trials.

Clinical trial results

4.11 In PEDFIC1, the proportion of positive pruritus assessments (a reduction of at least 70% in serum bile acid level from baseline or reaching 70 micromol/litre or less) compared to placebo after 24 weeks of treatment was statistically significantly greater in the odevixibat combined treatment arms (33%) than the placebo arm (0%). The results suggested a difference in response for people who had 40 microgram/kg/day of odevixibat compared with 120 microgram/kg/day, but this was not statistically significant. Also, the results were based on small patient numbers (the exact proportions are academic in confidence and cannot be reported here). There was a statistically significant greater proportion

of positive pruritus assessments (using the ObsRO instrument) in people in PEDFIC1 who had odevixibat (all doses; 54%) compared with placebo (29%). For people who continued to have odevixibat in PEDFIC2, the improvement in serum bile acid levels and pruritus was maintained. However, the greatest improvements were seen in those people who had had placebo in PEDFIC1 or were newly enrolled. The results also suggested some additional serum bile acid response to the 120 microgram/kg/day dose in people whose condition did not respond to the 40 microgram/kg/day dose in PEDFIC1 (the exact proportions are academic in confidence and cannot be reported here). The committee noted that the PEDFIC2 data used to determine the response to uptitration included 4 people with a follow up of only 24 weeks. Improvements in growth were also seen in PEDFIC1 for odevixibat compared with placebo and were maintained in people continuing odevixibat in PEDFIC2. The committee concluded that odevixibat was effective in reducing both serum bile acid level and pruritus in PFIC1 and PFIC2.

4.12 The committee next considered the clinical effectiveness of odevixibat by PFIC type. It recalled that, in PEDFIC1, only people with PFIC types 1 and 2 were enrolled. Serum bile acid response rates improved in both types, but the data suggested a potential difference in the response rates by type. However, the committee noted that patient numbers in the subgroups were small, that the trial had not been designed to detect a difference by type, and that no statistical comparisons by type had been done. The committee noted that 5 people in PEDFIC2 had PFIC3 and 1 had PFIC6. However, there was no data for odevixibat in PFIC4 and PFIC5, even though these are included in the marketing authorisation. At the last data cut, 80% (4 of 5) people with PFIC3 had a serum bile acid response according to the definition in PEDFIC2. However, the committee noted that the results of the subgroup analyses by type were based on small numbers and that there was very little evidence for PFIC types other

than types 1 and 2. So, it concluded that the clinical effectiveness of odevixibat by PFIC type was uncertain.

4.13 In PEDFIC1, the proportion of people who had a treatment-related adverse event was higher for odevixibat (33%, 14 of 32) than placebo (15%, 3 of 20). The committee noted that the proportion of people with any adverse effect during the treatment period was high at 83% (35 of 42) in the odevixibat arm and 85% (17 of 20) in the placebo arm. However, no serious adverse events related to odevixibat were reported in the phase 2 study, and PEDFIC1 and 2. The clinical experts explained that odevixibat is well tolerated in clinical practice. The main adverse events are gastrointestinal and may be alleviated in some people by using the lower starting dose. The company stated that no additional safety monitoring is needed for odevixibat, and there are no special precautions or warnings for its use. The committee concluded that odevixibat has an acceptable adverse event profile.

Generalisability of the evidence

4.14 The clinical experts considered that the evidence from PEDFIC1 and PEDFIC2 was broadly generalisable to the population with PFIC seen in England. However, the committee was aware of several potential differences between the clinical trial populations and NHS clinical practice. To enrol in both PEDFIC1 and 2, people needed to have a serum bile acid level of 100 micromol/litre or more and an average pruritis score of 2 or more on the company's ObsRO instrument. The committee noted that 5 people in PEDFIC1 and 3 people in PEDFIC2 had been excluded because they met the pruritus eligibility criteria but did not have a high enough serum bile acid level. The committee recalled that the aim of treatment is to reduce pruritus, so these people would likely have treatment in clinical practice. PEDFIC1 also excluded people with a previous lack of response to ileal bile acid transporter inhibitors and SBD within 6 months. The ERG flagged that odevixibat may also be used in

these people and that they were included in cohort 2 of PEDFIC2. The committee recognised that the population included in the company's trials may not fully reflect that in clinical practice. However, given the limited data available, it concluded that data from the full population of PEDFIC1 was suitable for decision making.

4.15 The committee recalled that, at the week 24 data cut in PEDFIC2, the maximum treatment duration with odevixibat was 48 weeks. The ERG noted that changes in long-term outcomes (including survival, reduced transplant rates or delays to liver transplant with odevixibat) would therefore not have been captured in the evidence base. The effect of treatment on serum bile acid level, pruritus and growth over a longer period was also unknown. The clinical experts explained that people would have odevixibat until they had a lack of response or intolerable side effects, which may be after many years. The committee concluded that the effect of odevixibat on long-term outcomes was unknown.

4.16 The committee recalled that the company's main trial evidence was limited to PFIC1 and PFIC2, and that there was no data for many of the less prevalent types. One clinical expert emphasised the rarity of the condition, estimating that 10 people at most were diagnosed with the most common type, PFIC2, at her clinic a year. Given that PFIC4, PFIC5 and PFIC6 account for a small proportion of all diagnoses, it is unlikely that further data could be collected on the rarer types in clinical trials. Without this data, it was not possible to estimate whether the treatment effect of odevixibat would differ between types of PFIC. The committee recognised the practical challenges of recruiting people with the rarer types of PFIC to clinical trials. It concluded that the generalisability of the evidence for odevixibat to rarer PFIC types was uncertain.

4.17 The committee recalled that the marketing authorisation for odevixibat specifies a starting dose of 40 micrograms/kg/day. The dose can be escalated to 120 micrograms/kg/day if there has not been an adequate

clinical response after 3 months of continuous therapy. The company explained that, by the time of the first committee meeting, it had not been possible to determine a real-life definition of an adequate clinical response or specific criteria for dose escalation. The clinical experts classed an adequate response to odevixibat as improvements in at least 2 of the 3 main PFIC outcomes: serum bile acid levels, pruritus and liver function tests. They acknowledged that a definition of response might vary among clinicians. However, they but explained that the dose of odevixibat would likely be increased if little or no improvement in these outcomes was seen. The committee also noted that the dosage of odevixibat given in the clinical trials was not based on response. People who had 40 micrograms/kg/day in PEDFIC1 and then went into PEDFIC2 had the high dose regardless of the previous response to treatment. Also, people enrolled in the PEDFIC2 cohort 2 started on high-dose odevixibat, whereas they would start on a lower dose in clinical practice. The clinical experts explained that the mechanism underlying response in PFIC was complex but expected the condition in some people to respond to dose escalation. The committee agreed that, without a definition of response, the generalisability of the clinical trials and response to dose escalation in clinical practice was uncertain.

Cost to the NHS and value for money

Economic model for PFIC

4.18 The company developed a semi-Markov model to estimate the cost effectiveness of odevixibat. The population included in the model was limited to people with PFIC1 and PFIC2, reflecting evidence from the PEDFIC1 study. The model health states included response and loss of response for serum bile acid, response and loss of response to PEBD, liver transplant, after liver transplant and death. Only people who had odevixibat could have a serum bile acid response, which the company assumed was always associated with an improvement in pruritus.

Following loss of response to odevixibat, people in the model did not have SBD, instead progressing straight to liver transplant. People having standard care with off-label medicines were assumed not to have a serum bile acid response and entered the model in the serum bile acid loss-of-response health state. They could then progress to liver transplant from any of the loss-of-response health states, but not from the PEBD response state. Most people remained in the liver-transplant health state for 1 cycle only. However, a small proportion of people in both arms remained for an additional cycle to represent people who had another transplant. The company assumed that people moved up to the higher dose of odevixibat if there was no response after 6 months of continuous treatment at 40 micrograms/kg/day.

4.19 The clinical experts highlighted that the pathway in the company's model differed from clinical practice because it did not include PEBD in the odevixibat arm. The committee recalled that a few people whose condition is not controlled by odevixibat may be offered PEBD before transplant. Also, the clinical experts highlighted that the model did not capture treatment differences for other types of PFIC, for example, that people with PFIC3 are less likely to have SBD (see section 4.5). They also highlighted that improvements in growth and liver function were important outcomes to people with PFIC and their families but had not been included in the company's modelling. The committee concluded that the basic model structure was appropriate for decision making, but that PEBD should have been included as an option in the odevixibat arm.

Clinical evidence in the model

4.20 The company used data from PEDFIC1 to populate the patient characteristics and serum bile acid response to odevixibat for people having the 40 micrograms/kg/day dose in the economic model. The company calculated the proportion of people having high-dose odevixibat in the model using the ratio between the people with a response at the low

dose and those with a response at any dose. For people having high-dose odevixibat, the model used the serum bile acid response at week 24 in PEDFIC2 for people whose condition had not responded to low-dose odevixibat in PEDFIC1. The committee noted the company's assumptions about high-dose odevixibat were calculated using data from few people. For example, only 4 people who did not respond to 40 micrograms/kg/day had week 24 data available at the cut-off to inform the response rates. The clinical experts explained that there was currently no way to predict what proportion of people would be having high-dose odevixibat in clinical practice. The committee concluded that there was significant uncertainty surrounding the proportion of people having high-dose odevixibat and the serum bile acid response in these people.

4.21 In people whose condition had responded to odevixibat, the company modelled loss of serum bile acid and pruritus response using the stopping rate from PEDFIC2. The ERG noted that people in the PEDFIC2 study who stopped odevixibat did so because of adverse effects, not because of a lack of serum bile acid response. This meant that the loss-of-response rate is likely to be higher in clinical practice than that modelled by the company. The clinical experts explained that people would be keen to keep having odevixibat if it improved pruritus. They thought people would only likely stop treatment if they had unbearable side effects or progression of liver disease. For this reason, the stopping rate in clinical practice was likely to be low and was therefore comparable to that in PEDFIC2. One clinical expert estimated that about 30% of people would stop odevixibat over time. The committee concluded that the long-term effectiveness of odevixibat was uncertain.

4.22 For the standard care arm, the probabilities for having PEBD and subsequent progression to a liver transplant were taken from the NAPPED natural history study. The committee noted that NAPPED was a global study, so the rates of PEBD seen were likely higher than those in

England, where this surgery is rarely done. The clinical experts emphasised that, because of the long waiting list for liver transplant, the frequency of PEBD in England might increase in the future. The company assumed that, in 5% of people, the response to PEBD would be lost in each cycle. This was based on clinical advice to the company that the loss of response for PEBD would be slightly higher than for that of odevixibat because of the complications associated with surgery. The committee agreed that this rate was uncertain but was aware that no alternative data sources existed. The committee recalled its earlier conclusion that PEBD should be included in the odevixibat arm. The company highlighted that a response to PEBD might differ in people who had previously had odevixibat. However, the committee noted that it had not been presented with clinical evidence to confirm this. It concluded that PEBD should have been included in both arms. It also concluded that the rates should be considered in exploratory analyses, if possible, informed by a data source that was clinically relevant to the NHS.

4.23 The company calculated the probability of liver transplant in people who had not had PEBD in both arms using data from native liver survival curves in NAPPED. The ERG flagged that this data included people whose condition both did and did not show a serum bile acid response to treatment. So, transplant rates for odevixibat would likely be higher than was modelled. In its base case, the ERG assumed equal rates of liver transplants in the health states for serum bile acid loss-of-response and PEBD loss-of-response. The clinical experts stated that this assumption was appropriate. The committee concluded that the ERG's probability of liver transplants was most appropriate for people who had not had PEBD.

4.24 The company modelled mortality rates using a variety of sources, which applied to both the odevixibat and standard-care arms in the model. For the acute post-transplant mortality rates (applied in the year of transplant in the model), the company used a meta-analysis of mortality rates from

10 PFIC studies reported in the literature. For the long-term mortality rates, applied in the model from the second year after transplant, the company used data from survival curves from 4 of these studies. It fitted an exponential distribution to this data. This gave an acute post-transplant mortality of 11.31% and a long-term post-transplant mortality of 1.94%. The ERG's analysis, which corrected several errors in the company model, and adjusted the meta-analysis output, produced an acute post-transplant mortality rate of 10.92% and long-term rate of 1.42%. The committee agreed with the ERG's corrections and considered its mortality rates most appropriate for decision making.

Costs applied in the model

4.25 The company applied the costs of odevixibat in the serum bile acid response state and for 6 weeks in the first cycle of the serum bile acid loss-of-response health state. Dosing was based on the average weight by age up to a weight of 55.5 kilograms. The company also applied a normal distribution to calculate the proportion in each weight category. The costs of off-label medicines were included in the loss-of-response health states for both arms because the company assumed that they would be used alongside odevixibat. Because there were no serious adverse events related to odevixibat in PEDFIC1 and 2, the company did not include costs for adverse events in its base case. It did, however, include costs for carers' lost productivity for everyone younger than 18 years in the model. It stated that odevixibat was expected to have a cost saving beyond the NHS and personal social services (see section 4.36). The committee agreed with the ERG that the inclusion of productivity costs was outside the NICE reference case. It preferred the ERG's analyses, which excluded productivity costs and included costs for commonly occurring treatment emergent adverse events in PEDFIC1.

4.26 The committee noted several areas of uncertainty in the company's costs. It recalled that the proportion of people who would have low- and high-

dose odevixibat in clinical practice was uncertain. It noted that high-dose treatment in the model was 3 times the dose (and therefore the cost) of low-dose treatment. This meant that the proportion on high-dose treatment was a large driver of cost effectiveness. The ERG also noted that the company's costs for PEBD included repeated surgeries for 67% of people, with equal costs applied to each surgery (same cost as initial procedure). The ERG stated that these assumptions were likely to be overestimates, so the cost of PEBD surgery in clinical practice would likely be lower. The ERG presented scenarios that varied the proportion of people on high-dose odevixibat and used lower costs for PEBD. The committee agreed that the company's costs were uncertain and considered both the company's base case and ERG's scenarios in its decision making.

Utilities

4.27 PEDFIC1 and PEDFIC2 collected Paediatric Quality of Life Inventory (PedsQL) data at baseline and week 24. This was mapped to EQ-5D-3L using a mapping algorithm from Khan et al. (2014). However, data was only available for a few people, so the company chose to use utility values from the literature in its base case. The company sourced utility values for odevixibat response from a study by Kamath et al. (2015). For loss of response, it used utility values of 0.91 from healthy children to represent serum bile acid response, and 0.83 from children with chronic intrahepatic cholestasis of any cause (of whom 51% had genetically confirmed PFIC). The ERG noted that, because of ongoing complications (including extra-hepatic features) and symptoms of PFIC, people whose condition has responded to odevixibat are unlikely to have the same quality of life as a healthy child. So, the company's utility values were higher than would be expected in clinical practice. The ERG preferred to use the utility values from the company's mapping study in its base case (0.858 for serum bile acid response and 0.697 for serum bile acid loss of response). The

committee agreed that the company's utilities were likely to be high and that values derived directly from the clinical trial were preferred.

4.28 For response and loss of response to PEBD, the company used the utility for healthy children from Kamath et al. (2015). However, it applied a disutility multiplier of 0.722 to represent the quality-of-life effect of having a stoma bag. This was taken from a study of adults with ulcerative colitis by Arseneau et al. (2006). For the PEBD loss-of-response health state, the company applied an additional disutility multiplier of 0.977 for short stature, reported in a study of children with chronic kidney disease by Al-Uzri et al. (2013). This resulted in utilities of 0.659 for PEBD response and 0.599 for PEBD loss of response. The company also presented scenario analyses using a stoma bag disutility of 0.945 from a colorectal cancer study by Hornbrook et al. (2011) and its own utility elicitation study, which used data from 2 carers of children with PFIC (the exact value is academic in confidence and cannot be reported here). The ERG chose to use a disutility multiplier of 0.833 in its base case, calculated by averaging the disutilities derived from the colorectal cancer and ulcerative colitis studies. The clinical experts explained that the stoma-related effect on quality of life is significant, especially in older children. This is because the disutility may be larger in them and they often refuse an external biliary diversion. One clinical expert also highlighted that stoma-related quality of life was likely to be better for someone with colorectal cancer or ulcerative colitis than for someone with a stoma bag collecting bile. This is because of problems arising from the irritant nature of bile. The patient experts highlighted that people with PFIC and carers have a very negative attitude to having a stoma bag, and that sometimes the surgery may not resolve the pruritus. The committee agreed that the disutility of living with a stoma bag was likely to be lower than both the company and ERG's preferred values, but higher than the utility derived by the company's elicitation study. It would have preferred to see analyses using alternative stoma

bag disutilities. However, it concluded that, in the absence of alternative sources, the ERG's utility value should be used for decision making.

4.29 In the model, the company assumed that most people have liver transplant did so because of uncontrolled pruritus. For this reason, both the company and ERG used a utility value of 0.710 in their base cases for liver transplant, that was derived from people with severe pruritus. To represent the quality of life for people with PFIC post-transplant, the company used a value of 0.850, mapped from PedsQL data in a systematic review of children having a liver transplant. The ERG chose to use a lower value of 0.798 for this health state. There was no utility for after liver transplant from the company's mapping study. So, it calculated the ratio of the utilities for after liver transplant and for odevixibat response from the literature. This ratio was then applied to the odevixibat response utility from the mapping study. The committee agreed that utilities mapped from the clinical trial were most appropriate. So, it concluded that the ERGs utility value for the post-liver-transplant health state were the most preferrable.

4.30 The company and ERG included a carer disutility of -0.05 in the PEBD response, serum bile acid loss-of-response and post-liver-transplant health states and a disutility of -0.1 for the PEBD loss-of-response health state. The committee recalled that the burden on carers could be substantial because children with PFIC often needed a significant amount of carer support. However, it noted that the disutility for carers had been sourced from NICEs technology appraisal guidance on nusinersen for treating spinal muscular atrophy and on dupilumab for treating moderate to severe atopic dermatitis. These conditions manifest in different ways to PFIC. The committee concluded that carer disutilities should be included in the modelling, but that the extent of any carer disutility in PFIC is uncertain.

Application of quality-adjusted life year (QALY) weighting

4.31 The committee understood that NICE's interim process and methods of the highly specialised technologies programme (2017) specifies that a most plausible incremental cost-effectiveness ratio (ICER) of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the size of the incremental therapeutic improvement. This is seen through the number of additional QALYs gained and by applying a 'QALY weight'. It understood that a weight of between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. The committee considered that there was uncertainty in both the company's and ERG's analyses. However, it concluded that the undiscounted QALY gains for the scenarios incorporating its preferred assumptions did not meet the criteria for applying a QALY weight.

Cost-effectiveness analysis results

4.32 The company and NHS England have agreed a confidential commercial discount for odevixibat. All cost-effectiveness results of the economic analysis incorporating this discount, along with any comparator discounts, are confidential, so the ICERs cannot be reported here.

4.33 The committee noted that using the ERG's preferred assumptions considerably increased the ICERs when compared with the company's base case. However, both base cases provided ICERs above the threshold considered to provide value for money in the context of a highly specialised service when the confidential discounts for odevixibat and comparators were applied. The ERG noted a counterintuitive relationship between the clinical and cost effectiveness of odevixibat. This meant that scenarios with a higher loss of response or lower response rates to odevixibat resulted in lower ICERs. This was likely because the liver-

transplant health state (where most costs were accrued in the standard-care arm) had a more favourable cost profile than the serum bile acid response health state (where most costs were accrued in the odevixibat arm). So, moving people to the liver-transplant health state reduced the incremental costs between arms and in turn lowered the ICER. The committee recalled the uncertainty in the company's assumptions surrounding the response to odevixibat and the proportion of people who lost response. It considered the ERG's scenarios that varied these parameters, noting that the scenarios remained above the cost-effectiveness threshold when confidential discounts were applied. The committee concluded that both the company's and ERG's cost-effectiveness results were uncertain.

4.34 The committee considered the following assumptions to be the most appropriate for decision making:

- including PEBD in the odevixibat arm at the same rate as for standard care
- using the same probability of liver transplant for odevixibat and PEBD loss-of-response health states
- using utility values from the ERG's base case
- using mortality rates for the acute and long term after liver transplant from the ERG's analyses
- excluding carer productivity costs
- including costs of common adverse events from PEDFIC1
- applying a 3.5% discount for costs and benefits, with no additional QALY weighting.

Using these assumptions, the cost-effectiveness results for odevixibat compared with standard care were considerably higher than the threshold normally considered an effective use of NHS resources in a highly specialised technology.

4.35 The committee also considered that there was considerable uncertainty surrounding the cost effectiveness of odevixibat for people with PFIC. The committee recognised that:

- It had been presented with very limited data for people with PFIC types other than PFIC1 and PFIC2.
- There was no data for odevixibat when used before or compared directly with PEBD.
- The long-term effectiveness of odevixibat on survival, time to liver transplant and use of SBD was unclear.
- The proportion of people whose condition stopped responding to treatment and the response rates to high-dose odevixibat were uncertain.
- There was no evidence that used the dose escalation schedule in the marketing authorisation that would be used in NHS practice.

The committee acknowledged that some of these uncertainties could be resolved with data collection. It was aware that the PEDFIC2 study was ongoing and could provide further data on survival outcomes, liver transplant rates and alternative utility values for people having high-dose odevixibat. It was also aware that the company's planned indirect comparison would also provide data on the effectiveness of odevixibat compared with PEBD. The committee noted that a managed access agreement could resolve uncertainty about the proportion of people having high-dose odevixibat in clinical practice and previous PEBD usage. However, because the company's stopping rate for odevixibat was low, it was unlikely that this uncertainty could be resolved within the specified timeframe. The committee noted that a registry study had been requested by the regulator but acknowledged there were practical challenges in adapting this to collect data in NHS clinical practice. The committee agreed that, had odevixibat shown a plausible potential for cost effectiveness, managed access might have been a valid option.

However, it noted that all company and ERG scenarios were substantially above the threshold normally considered a good use of NHS resources for highly specialised services. So, because there was no plausible potential for odevixibat to be cost effective, a managed access agreement could not be considered. The committee concluded that it was unable to recommend odevixibat for treating PFIC.

Impact of the technology beyond direct health benefits and on the delivery of the specialised service

4.36 The company stated that odevixibat would result in benefits beyond those for the NHS and personal social services. The committee understood from the patient experts that children with PFIC need significant carer support, which can have a considerable effect on the quality of life of families. It recalled that carers frequently had to reduce their working hours or stop working because of the number of hospital visits and sleepless nights. The demands of caring for a child with PFIC after surgery or transplant also needed large periods of time off work, which could have a severe financial impact on families. For this reason, the company included costs for lost productivity of carers in its base case (see section 4.25). The clinical experts stated that odevixibat could reduce the burden for families and carers because it had the potential to:

- lessen the number of hospital visits needed
- remove the need for a SBD
- delay the time to liver transplant.

They highlighted that, because there was evidence that odevixibat improved pruritus, it could also lessen the psychological effect of the condition for people with PFIC, carers and siblings. The committee noted that people with PFIC who have odevixibat would still:

- need to regularly monitor for signs of reduced liver function
- need to continue to eat an optimised diet to avoid malnutrition

- most likely still need liver transplant at some point in their lives.

For these reasons, they would also most likely still need some support from carers. The committee recalled that the company and ERG had not applied carer disutilties in the serum bile acid response state (see section 4.30). So, people whose condition had responded to odevixibat were assumed to need less care than those in whom response had been lost. The committee agreed that PFIC affects patients beyond the direct health benefits and that odevixibat had the potential to reduce the burden for carers. However, it concluded that these benefits had been captured in the modelling.

Delivery of specialised services

4.37 The company stated that treatment with odevixibat would be started and supervised by clinicians experienced in managing PFIC. It highlighted that the only additional monitoring needed with odevixibat is to determine response, and that no additional safety monitoring is needed. The committee noted that PFIC is currently managed in 3 specialist centres in England. The representative from NHS England confirmed that odevixibat would be started at specialist centres, with the potential to consider monitoring by local healthcare providers if safe and useful. The representative confirmed that additional infrastructure or staff training would not be needed to introduce odevixibat in England. The committee concluded that, if approved, odevixibat would be administered at specialist centres under the existing arrangements for people with PFIC.

Other factors

Innovation

4.38 The company stated that it considered odevixibat to be a step change in the treatment of PFIC. This was because there are currently no licensed treatments for the condition, and current options have a high failure rate and can be invasive. The company highlighted that odevixibat is easy to

administer in capsule form and can be sprinkled on to food for younger children. The clinical experts agreed that odevixibat was innovative because it is the first drug to both improve pruritus and limit progression of liver disease. They also flagged that the improvements in growth in people having odevixibat are important. The committee noted that odevixibat has a novel mechanism of action, no drug interactions and manageable side effects. It recalled that there was high unmet need in this population. It also noted that odevixibat significantly reduced pruritus and serum bile acid levels in the randomised controlled trial compared with standard care. It recognised that odevixibat was innovative.

Equalities

4.39 The committee noted that the population for which odevixibat is indicated includes children and young people. It discussed the need to balance the importance of improving the lives of children and their families with fairness to people of all ages. It noted the principles that guide the development of NICE guidance and standards. This emphasises 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 acknowledged and considered the nature of the population as part of its decision making.

Conclusion

4.40 The committee recalled its earlier decisions and discussed the recommendation it could make for odevixibat for treating PFIC. It took into account the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits. The committee acknowledged that PFIC, and particularly pruritus, has a substantial effect on the quality of life of people with PFIC, and their carers and families. It noted that the clinical evidence suggested that odevixibat provides clinical benefit by reducing serum bile acid levels and pruritus compared with placebo. However, it recalled that there was no evidence presented for

the rarer types of PFIC or comparing odevixibat with PEBD. In addition, there is no data on the anticipated NHS dosing schedule, and no agreed criteria for dose escalation after 3 months if there is not an adequate response. The short follow-up period in the clinical trial means that there is uncertainty about the longer-term outcomes such as time to, and need for, liver surgery and overall survival rates. The committee agreed that odevixibat likely reduces serum bile acid levels and pruritus in people with PFIC1 and PFIC2, but that its effectiveness in clinical practice is uncertain.

4.41 The committee considered that the company's model structure was generally acceptable for decision making. However, it agreed that PEBD should have been included in the model as a subsequent treatment for people who have odevixibat, even though it is rarely used in clinical practice. The committee also considered that there were uncertainties associated with several parameters used in the model. This was particularly so for the size of the disutility associated with stoma bag use and the proportion of people who would be having high-dose odevixibat in clinical practice. It agreed that a 3.5% discount rate for health and benefits with no additional QALY weighting was appropriate for decision making. When using the committee's preferred assumptions and applying the confidential discounts, the ICER was substantially above the range considered to provide value for money in the context of a highly specialised service. The committee acknowledged that odevixibat is a high-cost technology and that uncertainties remained about the clinical evidence. It agreed that some of these uncertainties could be resolved with further data collection in a managed access agreement. However, none of the company or ERG scenarios were within the threshold considered a cost-effective use of resources for highly specialised technologies. So, the committee did not consider that odevixibat had the potential to be cost effective. As such, it could not be considered for a

managed access agreement. The committee concluded that it was unable to recommend odevixibat for PFIC.

5 Proposed date for review of guidance

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

Paul Arundel
Chair, highly specialised technologies evaluation committee
September 2021

6 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

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

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.

NICE project team

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

Emma Douch
Technical lead

Carl Prescott
Technical adviser

Joanne Ekeledo
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