The cost-effectiveness of odevixibat (Bylvay®) for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of odevixibat for the treatment of progressive familial intrahepatic cholestasis. Following assessment of the Applicant's submission, the NCPE recommends that odevixibat not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The HSE asked the NCPE to carry out an evaluation of the Applicant's (Albireo Pharma) Health Technology Assessment of odevixibat. The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013

National Centre for Pharmacoeconomics **March 2023**

Summary

On the 16th August 2022 Albireo Pharma submitted an economic dossier on the cost-effectiveness of odevixibat (Bylvay®) for the treatment of progressive familial intrahepatic cholestasis (PFIC) which is a rare, heterogeneous group of liver disorders resulting from defects in the secretion of bile from hepatocytes to the biliary canaliculi. It is inherited as an autosomal recessive trait resulting in pruritis and malabsorption followed by progression to liver failure. Progressive familial intrahepatic cholestasis is subdivided according to the genetic defect, clinical presentation, laboratory findings and liver histology. There are three main subtypes, PFIC1, PFIC2 and PFIC3 although at least three other subtypes have been described i.e. PFIC4, PFIC5 and PFIC6. Two-thirds of all cases of progressive familial intrahepatic cholestasis are due to PFIC1 and PFIC2 with PFIC3 accounting for approximately one-third of cases.

The rate of progression to end-stage liver disease varies by subtype occurring in the first few years of life in PFIC2, in the first decade in PFIC1 and in the first or second decade of life in PFIC3. Hepatocellular carcinoma is seen in PFIC2. Growth delay, failure to thrive, vitamin A,D,E,K deficiency and reduced quality of life are common manifestations of progressive familial intrahepatic cholestasis. Survival in patients with PFIC who do not undergo surgical biliary diversion (SBD) or liver transplantation is approximately 50% at age 10 years and almost 0% at the age of 20 years. Diagnosis usually requires a combination of clinical evaluation, liver biopsy and imaging. In Ireland genetic testing is used to aid the diagnosis of PFIC. Most patients with PFIC will eventually require liver transplantation.

Marketing authorisation for odevixibat was granted by the European Medicines Agency (EMA) on the 16th July 2021 for the treatment of PFIC in patients aged 6 months or older. It is a small molecule, second-generation inhibitor of the ileal bile acid transporter (IBAT) resulting in a reduction in the level of total serum bile acids. The recommended dose of odevixibat is 40 µg/kg administered orally once daily and the pharmaceutical formulation is in the form of hard capsules produced in four strengths: 200µg, 400µg, 600µg and 1,200µg. The capsules may be swallowed or opened and sprinkled on food. If an adequate clinical response has not been achieved after three months of continuous therapy the dose may be

increased to 120 µg/kg/day. An adequate response is suggested as an improvement in at least two of the following parameters: serum bile acid (sBA) levels, liver function tests and pruritis. There are no Irish specific treatment guidelines for PFIC however it is anticipated that odevixibat will be a first-line treatment used prior to surgical intervention i.e. partial external biliary diversion (PEBD) and liver transplantation.

1. Comparative effectiveness

The primary evidence for the efficacy and safety of odevixibat for the treatment of progressive familial intrahepatic cholestasis is based on two phase 3 studies i.e. PEDFIC1 and a 24 week interim analysis of the on-going phase 3 open-label extension study PEDFIC2 which is evaluating treatment with odevixibat 120 µg/kg/day. As well as providing long-term data in patients that participated in PEDFIC1 the PEDFIC2 study is investigating efficacy, safety and tolerability in an additional cohort that includes patients of any age with any type of PFIC.

Inclusion criteria for the PEDFIC1 study included (a) patients aged 6 months to 18 years with a clinical diagnosis of PFIC1 or PFIC2 and genetic confirmation of biallelic pathogenic mutations in the ATP8B1 (i.e. PFIC 1) or ABCB11 (i.e. PFIC 2) genes (b) elevated serum bile acids (≥ 100 µmol/l) (c) history of significant pruritis as determined by the investigator and (d) an average caregiver reported observed scratching score of 2 or greater. Patients were randomly assigned to once a day oral placebo, odevixibat 40 µg/kg or odevixibat 120 µg/kg. Two primary endpoints included (a) proportion of positive pruritis assessments (PPAs i.e. scratching score of ≤ 1 or ≥ 1 – point decrease as assessed by caregivers using the Albireo observer-reported outcome [ObsRO] PRUCISION instrument) over 24 weeks and the proportion of patients with serum bile acid response (i.e. serum bile acids reduced by ≥ 70% from baseline or concentration ≤ 70 µmol/l) at week 24.

Sixty two patients (median age 3.2 years, 55% female, mean weight 16.4kg) were randomly allocated to placebo (n=20), odevixibat 40 µg/kg/day (n=23) or odevixibat 120 µg/kg/day (n=19). For patients treated with odevixibat 29% had PFIC1 and 71% had PFIC2 and 76% were treated with UDCA at baseline. Model adjusted mean proportion of PPAs was

significantly higher with odevixibat versus placebo (55% [SE 8] in the combined odevixibat group versus 30% [SE 9] in the placebo group, model-adjusted mean difference 25% [95% confidence interval (CI) 8.5 – 41.5]; p = 0.0038). The percentage of patients with a serum bile acid response was significantly higher with odevixibat versus placebo (14 [33%] of 42 patients in the combined odevixibat group versus none of 20 in the placebo group; adjusting for stratification factor the proportion difference was 30.7% [95% CI 12.6 – 48.8; p = 0.003]). Treatment with odevixibat led to reductions from baseline in standard liver function tests (e.g. ALT) and to improvements in baseline height and weight Z-scores however these were not statistically significant at weeks 12 or 24. Treatment with odevixibat improved sleep parameters for patients based on caregiver-reported information. A post hoc analysis comparing results for the 40 µg/kg/day and the 120 µg/kg/day odevixibat doses did not show any statistically significant differences in the proportion of responders.

The PEDFIC2 trial is an on-going 72 week phase 3, multi-centre, open-label extension study to investigate the long-term efficacy and safety of a 120 µg/kg daily dose of odevixibat in patients with progressive familial intrahepatic cholestasis. It includes two cohorts (a) children with PFIC types 1 and 2 who participated in the PEDFIC1 trial and (b) patients with PFIC who have elevated serum bile acids and cholestatic pruritis who did not meet the eligibility criteria for PEDFIC1. Patients who could not tolerate the 120 µg/kg/day dose had the option to down-titrate to the 40 µg/kg/day dose. The primary endpoint was change from baseline in serum bile acids after 72 weeks of treatment (reach ≤ 70 µmol/l or a reduction of 70%). Secondary endpoints included proportion of positive pruritis assessments using ObsRO instrument, all-cause mortality, number of patients undergoing biliary diversion or listed for liver transplantation, changes in the following: growth, AST to platelet ratio, antipruritic medication and paediatric end-stage liver disease. A total of 71 patients enrolled in PEDFIC2 and interim results at week 24 presented in the submitted economic dossier indicated that treatment with odevixibat 120 µg/kg/day led to continued improvement in serum bile acid levels. Improvements in pruritis, scratching severity, sleep parameters, height and weight scores were also reported.

Information in relation to supporting studies was also provided including the NAtural course and Prognosis of PFIC and Effect of biliary Diversion (NAPPED) study which has the largest

genetically defined cohort of PFIC patients to date, providing retrospective analysis of 130 PFIC1 and 264 PFIC2 patients in over 50 centres worldwide.

2. Safety

In the PEDFIC1 study 35 (83%) of the 42 patients receiving odevixibat experienced treatment-emergent adverse events, a similar rate was observed in the placebo group. The majority of adverse events were mild or moderate in severity. The most commonly reported adverse events (occurring in ≥ 10% of patients) were diarrhoea or frequent bowel movements (31% of odevixibat patients versus 5% in the placebo group), fever (29% versus 25%), upper respiratory tract infection (19% versus 15%), vomiting (17% versus none from the placebo group), increased ALT (14% versus 5%) and increased bilirubin (12% versus 10%). One patient in the 120 µg/kg/day treatment group discontinued treatment due to diarrhoea. There were no deaths during the study. The adverse event profile was similar in PEDFIC2 where three patients discontinued treatment with odevixibat 120 µg/kg/day due to treatment-emergent adverse events. No deaths occurred during the PEDFIC2 study. There was no indication of a dose-dependent effect on the observed adverse events.

3. Cost effectiveness

The patient population included in the economic model were those with progressive familial intrahepatic cholestasis type 1 (PFIC1) and type 2 (PFIC2). Despite clinical differences in these two subtypes a joint population approach was used. The intervention under assessment was odevixibat 40 µg/kg administered orally once daily. The dose may be escalated to 120 µg/kg/day if an adequate clinical response was not achieved after three months of continuous therapy at the lower dose. The comparator in the economic analysis was the current standard of care, which included partial external biliary diversion (PEBD). The cost-effectiveness model was a seven-state Markov model developed in Microsoft Excel to capture the differences in costs and health outcomes between odevixibat and the standard of care.

The structure of the model included seven health states: (i) pruritis response with or without a serum bile acid response (ii) loss of pruritis response with or without loss of serum bile acid response (iii) post partial external biliary diversion (PEBD) pruritis response with or without a serum bile acid response (iv) post-PEBD, loss of pruritis response with or without loss of serum bile acid response (v) liver transplantation (vi) post liver transplantation and (vii) death. A lifetime horizon (maximum age of 100 years) was chosen with a cycle length of one year and half-cycle correction was implemented. Patient demographics at baseline were based on the PEDFIC1 study population. When entering the model, patients are distributed across the response (pruritis with/without serum bile acid response) and non-response states depending on whether they receive odevixibat or standard of care, respectively. Progression to PEBD and liver transplantation is driven by the exacerbation of pruritis resulting from elevated bile acids. Patients can progress to liver transplantation before or after PEBD. The primary benefit of odevixibat is captured in the delayed time to liver transplantation and partial external biliary diversion (PEBD). The increased mortality in progressive familial intrahepatic cholestasis in the standard of care arm is captured by acute and long-term liver transplantation mortality as well as increased pre-liver transplantation mortality. Survival curves from the NAPPED study were used to estimate the transition to PEBD and liver transplantation. Where transitions were based on survival data, exponential models were used to estimate a constant transition rate. Background mortality was modelled using general population life tables for Ireland. It was assumed that there was only excess mortality in the health states with no response.

Utility values for patients without partial external biliary diversion were derived from a study by Kamath et al. who investigated health related quality of life in children with Alagille syndrome, healthy children and other liver disease cohorts including chronic intrahepatic cholestasis using PedsQL. The PedsQL scores were mapped to the EQ-5D using the algorithm by Kahn et al. Utility values for responders were assumed to be equal to those for healthy individuals and values for non-responders were similar to patients with chronic intrahepatic cholestasis. A disutility of a stoma bag was applied to derive an ‘after PEBD’ utility score. Utilities associated with liver transplantation were also informed by the published literature. Caregiver disutilities were applied in a scenario analysis and were derived from previous NICE technology appraisals. Direct medical costs from the HSE perspective were

incorporated into the model and included: drug acquisition and administration costs for intervention and standard of care, disease management costs, resource use and adverse event costs. For the base case a discount rate of 4% was applied to both health outcomes and costs. The model reports life years, quality adjusted life years (QALY) and costs per treatment cohort as well as the incremental cost-effectiveness ratios (ICERs). The analysis was conducted from the perspective of the Health Service Executive (HSE).

A deterministic analysis of the cost-effectiveness of odevixibat versus standard of care was associated with incremental costs of €3,374,154 and an incremental quality adjusted life-year (QALY) of 1.51 resulting in a base case incremental cost-effectiveness ratio (ICER) of €1,276,515/QALY. Probabilistic analysis resulted in an ICER of €1,221,269/QALY which was similar to the deterministic ICER. The probability of odevixibat being cost-effective at the €45,000/QALY threshold was 0%. A deterministic sensitivity analysis was also presented. The parameters that impacted the cost-effectiveness of odevixibat versus standard of care to the greatest extent included: discount rates, disutility of stoma bag, health PedsQL school score and post liver transplant PedsQL school score.

4. Budget impact

Odevixibat is an oral therapy provided as capsules containing 200µg, 400µg, 600µg and 1,200µg where the price to wholesaler per pack of 30 capsules is €3,490.12, €6,980.57, €10,470.68 and €20,941.36 respectively. The recommended dose of odevixibat is 40µg/kg administered orally once daily. The dose may be increased to 120µg/kg/day with a maximum daily dose of 7,200µg per day. It is anticipated that 8 patients would be treated in year 1 increasing to 14 patients in year 5 resulting in a 5 year gross drug budget impact of €17.34 million. The 5 year net drug budget impact was considered equal to the gross drug budget impact. There was uncertainty in relation to any potential cost-offsets.

5. Conclusion

This assessment demonstrates that odevixibat is not cost-effective for the treatment of progressive familial intrahepatic cholestasis in patients 6 months or older. The NCPE recommends that odevixibat not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.