NCPE Assessment Summary

Maralixibat (Livmarli®)

HTA ID: 25001

30 March 2026

Applicant: Mirum Pharmaceuticals

Maralixibat is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) two months of age and older

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of maralixibat (Livmarli®) for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) two months of age and older.

Following assessment of the Applicant's submission, the NCPE recommends that maralixibat (Livmarli®) not be considered for reimbursement for this indication, unless cost effectiveness can be improved relative to existing treatments. *

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Mirum Pharmaceuticals) Health Technology Assessment of maralixibat (Livmarli®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative 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.

Summary

In August 2025, Mirum Pharmaceuticals submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of maralixibat (Livmarli ®) for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) two months of age and older. Mirum Pharmaceuticals is seeking reimbursement of maralixibat for this indication on the High-Tech Drug Arrangement.

Alagille syndrome (ALGS) is a genetic disease with a wide variety of clinical manifestations. ALGS can impact multiple organs including the liver and heart. People with ALGS may have only mild symptoms and have a normal life expectancy, but some have severe and even life-threatening complications. Cholestasis is the most common symptom, where bile flow is impaired due to a lack of bile ducts, and often develops during the first three months of life. When bile flow is reduced or stops completely, it can lead to poor weight gain and growth deficiencies, and an excess of toxins in the body. Cholestasis causes jaundice, pruritus (itching), xanthomas (bumps on the skin from fat deposits), increased serum concentration of bile acids and growth failure. Pruritus is the most debilitating symptom, affecting all aspects of a child's life including sleep, appetite, education, relationships, and ability to take part in everyday activities. Severe and unremitting pruritus is present in approximately 80% of cases at 2 years.

Current treatment for ALGS focuses on alleviating symptoms. Treatments used to reduce itching include ursodeoxycholic acid, rifampicin and naltrexone, and are most commonly used as standard of care in Ireland. Clinical opinion has also suggested that odevixibat is used in a small number of cases. If ALGS symptoms do not respond to drug therapies, a partial biliary diversion may be carried out although this is rare in Ireland. In some cases symptoms resolve over time, but for others a liver transplant may be needed.
Maralixibat is licensed to treat cholestatic pruritus, the most common symptom of Alagille syndrome. Maralixibat is a minimally absorbed, reversible, potent, selective inhibitor of the ileal bile acid transporter (IBAT). By inhibiting IBAT, more bile acids are excreted in the faeces, leading to lower levels of bile acids systemically, thereby reducing bile acid mediated liver damage. The recommended target dose is 380mcg/kg once daily via oral solution. The

SpC states that alternative treatment should be considered in patients for whom no treatment benefit can be established following three months of continuous daily treatment with maralixibat.

1. Comparative effectiveness of maralixibat

The pivotal clinical trial ICONIC (LUM-001) was a long-term, open-label phase IIb study with a double-blind, placebo-controlled randomised withdrawal period, designed to evaluate the safety and efficacy of maralixibat in participants aged 12 months to 18 years inclusive. From baseline to Week 48, the study comprised an 18-week open-label run-in period (6-week dose escalation and 12-week stable dosing), a four-week randomised, double-blind, placebo-controlled drug withdrawal period, a 26-week stable dosing period at doses of up to 380 mcg/kg/day. The primary efficacy endpoint was mean change from Week 18 to Week 22 of fasting sBA levels in participants who previously responded to maralixibat treatment (as defined by a reduction in sBA ≥ 50% from baseline to Week 12 or Week 18). Other efficacy outcomes included change in pruritus assessed using the Itch Reported Outcome (ItchRO) observer (Obs) and patient (Pt) tools and health related quality of life (HRQoL) as measured by the Paediatric Quality of Life Inventory (PedsQL) total score (parent) and the PedsQL Multidimensional Fatigue Scale score (parent). Participants were subsequently eligible for an optional long-term treatment period from Week 49. After Week 100 of the open-label extension, to explore efficacy and safety of higher maralixibat doses, 14 of 16 participants with sBA levels of more than 8 micromol/L or ItchRO(Obs) ≥ 1.5 increased maralixibat doses to 380mcg/kg twice per day. This dose is not licensed for use, as the maximum dose licensed within the marketing authorisation is 380mcg/kg once daily.

The intention-to-treat (ITT) population comprised 31 participants. The modified ITT population comprised 15 participants considered to be responders (i.e., achieved a reduction in sBA ≥ 50% from baseline to Week 12 or Week 18). There was a statistically significant mean difference in change from Week 18 to Week 22 in sBA levels between the maralixibat and placebo groups in the modified ITT population (-117.28, 95% CI -232.4, -2.2, p-value 0.0464).

The Least Squares (LS) mean difference between the maralixibat and placebo groups for the change in the ItchRO(Obs) weekly average morning severity score was –1.48 (95% CI, –2.12

to –0.84; P < 0.0001), in favour of maralixibat. The LS mean difference between the maralixibat and placebo groups from Weeks 18 to 22 for the change in ItchRO(Pt) weekly average morning severity score was –1.98 (–3.01 to –0.97; P = 0.0013), in favour of maralixibat. The LS mean difference from Weeks 18 to 22 in the PedsQL total score (parent) between the maralixibat and placebo groups was 2.33 (95% CI, –10.08 to 14.75; P = 0.7018). A longer-term improvement in HRQoL was demonstrated by PedsQL scores up to 48 weeks however this part of the trial was open label, non-randomised and thus potentially subject to bias.

Key limitations of the ICONIC trial:

- The primary endpoint of the ICONIC trial was based on a surrogate outcome (sBA levels) assessed over a short-term period. It is unclear whether reduction in sBA levels will result in significant improvement in pruritus in patients with cholestatic liver diseases. Moreover, evidence from the literature to support a relationship between sBA level and pruritus severity is highly uncertain.
- Data from ICONIC showed an association between decreased fasting sBA levels and improvement in pruritus scores as assessed by the ItchRO(Obs) and ItchRO(Pt) weekly morning severity scores. However, the data were descriptive in nature, and the assessment was conducted post hoc on a small number of patients (n = 28, excluding participants who discontinued due to adverse events).
- Dose escalation, outside that permitted within the licence for maralixibat, was observed in the ICONIC trial. After Week 100, 14 of 16 participants remaining in the study, who had sBA levels above the upper limit of normal or who had pruritus symptoms, received 380 mcg/kg maralixibat twice daily.
- It was not determined that the use of maralixibat in patients with ALGS was associated with any improvements in quality of life.

Supportive studies:

Two double-blind, phase II studies, IMAGO and ITCH (and their respective extension studies), provided supportive evidence for maralixibat. ITCH was a randomised, double-blind, placebo-controlled study in children (12 months to 18 years) with ALGS (based in the US and Canada; n=37). The primary efficacy endpoint was change from baseline in pruritus as

measured by ItchRO(obs) (Week 13 or date of study discontinuation). IMAGINE II was a multicentre extension study to evaluate the long-term safety and durability of the therapeutic effect of maralixibat in participants from the ITCH trial. The IMAGO trial was a randomised, double-blind, placebo-controlled study to evaluate the safety and tolerability of maralixibat in children aged 12 months to 18 years (based in the UK; n=20). The primary efficacy endpoint was change from baseline to Week 13 in fasting sBA levels. IMAGINE was a multicentre extension study to evaluate the long-term safety and efficacy of maralixibat in participants from the IMAGO trial.

The Global Alagille Alliance Study (GALA) is an international database of clinical, genetic and laboratory data in children and young adults with ALGS. The GALA clinical research database allowed for the selection of a balanced external comparator group to the maralixibat cohort (from the ICONIC, IMAGINE and IMAGINE II trials) to evaluate long term clinical outcomes such as event free survival (EFS), which were not available from the pivotal trial. The Review Group noted several issues with this comparison, which impacted on the certainty of the results, namely, potential selection bias between comparator groups, imbalance in baseline characteristics between both cohorts (sBA data was missing for 85% of patients included), also it was unknown how severe cholestatic pruritus was in the absence of information on pruritus severity at baseline, which is a significant limitation. Other important prognostic factors besides pruritus severity, such as patients' history of disease, previous treatments, duration of disease, and comorbidities, were unavailable. Therefore, it is highly likely that many other confounding factors were still unaccounted for, particularly the disease severity, which could have a significant impact on long-term clinical outcomes such as liver transplant or death. Therefore, the effect of maralixibat on long term clinical outcomes is highly uncertain.

2. Safety of maralixibat

The safety profile of maralixibat is based on a pooled analysis of data from the five clinical studies of maralixibat in patients with ALGS (n=86) aged between 1 and 17 years. The median duration of exposure was 2.5 years. The most frequently occurring adverse event (AE) in patients with ALGS aged 12 months and older were diarrhoea (36%) followed by abdominal pain (29.1%). The most frequently occurring AE in patients with ALGS younger

than 12 months of age was diarrhoea. The safety profile of maralixibat is consistent across all indications and age groups.

3. Cost effectiveness of maralixibat

Methods

The Applicant developed a cohort multi-state Markov model which included eight mutually exclusive health states: responder, non-responder, cirrhosis, portal hypertension, ascites, liver transplant, post liver transplant and death. Transitions to improved health states were not permitted. The cycle length was 12 weeks, and half cycle correction was applied. The starting age of patients in the model was two months, based on the minimum licensed age. The model had a lifetime horizon of 100 years. In each cycle, patients accrued quality-adjusted life years (QALYs) and incurred costs specified for the health-state occupied.

The model intervention was maralixibat and the comparator (herein referred to as standard of care [SoC]) was a weighted basket comparator comprising off-label therapies used; ursodeoxycholic acid (71.0%), rifampicin (80.60%), sertraline (3.2%) and naltrexone (9.70%). The Applicant was asked to provide a comparison to odevixibat (also an IBAT inhibitor). The Applicant declined to provide this owing to issues with comparative trial design which would introduce too much uncertainty to an indirect treatment comparison. The treatment effects captured included delay in liver-disease progression and death. The key efficacy input was response to maralixibat treatment, assessed by sBA reduction. The Review Group considered that the severity of itch was probably more relevant to patients as a measure of response. When patients were deemed non-responders in the model all further transitions to downstream health states were equivalent for both the maralixibat and SoC arms.

Transitions from the responder health state for the maralixibat arm were informed by the ICONIC trial whereby response was defined as a reduction in sBA of ≥50% from baseline to 12 weeks (open-label run-in phase) in the first model cycle. The Applicant assumed discontinuation following the first cycle based on the observed discontinuation rate in the first 18 weeks (open-label phase) of the ICONIC trial. Patients receiving SoC were assumed to have a 0% response rate following the first cycle. Transition probabilities for downstream

health states were informed by published observational and retrospective studies.

The effect of maralixibat on long term clinical outcomes was informed using an unanchored matched comparison between the pooled data from the ICONIC, IMAGINE, and IMAGINE II trials and the GALA cohort. The Applicant used a hazard ratio (HR) of 0.305 (95% CI 0.19 to 0.49) to model OS (using EFS as a surrogate) between responders and non-responders.

The primary health outcome of the model was the QALY as per national guidelines. HRQoL values were applied to each health state. The impact of AEs on HRQoL was generally not included; the Applicant assumed they were largely mild and transient. The impact of abdominal pain on HRQoL was applied to the maralixibat arm, informed by published literature. The ICONIC trial collected PedsQL data which the Applicant did not map to the EQ-5D, stating some domains were not captured in the trial. For this reason, a vignette study was conducted by the Applicant using EQ-5D-5L and time trade-off valuation. The Applicant used HRQoL values from the vignette study for the responder, non-responder, liver transplant and post liver transplant health states. HRQoL values for the cirrhosis, portal hypertension and ascites health states were derived from published literature. The HRQoL values were not mapped to the EQ-5D-3L (and thus did not align with NCPE guidance). The impact on caregiver HRQoL, obtained from the vignette study, was included in the Applicant base case.

The model included drug acquisition costs for maralixibat and SoC. Other healthcare resources were aggregated as health state-specific costs and included hospital outpatient appointments. A palliative care cost was applied on entering the death state.

In order to explore the impact of the uncertainties highlighted the Review Group made a number of changes to the Applicant base case. These included the starting age of patients in the model, the source of data used to inform mortality transitions, the source of data used to inform HRQoL values for the responder and non-responder health states as well as how discontinuation is applied in the model. Inclusion of caregiver HRQoL was explored as a scenario within the NCPE adjusted base case. The impact on the ICER due to these changes was appreciable. The Review Group consider that even with the significant price decrease

estimated by the applicant of 90% for cost effectiveness to be achieved, uncertainties in cost effectiveness remains given the uncertain parameters.

Results

Table 1 and Table 2 provide an overview of the deterministic incremental cost-effectiveness ratios (ICERs) generated under the Applicant and NCPE base case assumptions, respectively.

Table 1: Applicant base case incremental cost-effectiveness results [a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
SoC	81,582	2.00	-	-	-
Maralixibat	384,055	3.13	302,473	1.13	267,553

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care
Costs and outcomes are discounted at 4.0%
a Corresponding probabilistic ICER using 1,000 iterations =€270,656/QALY. Figures in the table are rounded, and so calculations may not be directly replicable

Table 2: NCPE adjusted base case incremental cost-effectiveness results [a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
SoC	85,072	12.10	-	-	-
Maralixibat	1,725,520	12.64	1,640,447	0.53	3,070,590

ICER: incremental cost-effectiveness; QALY: quality-adjusted life year; SoC: standard of care
Costs and outcomes are discounted at 4.0%
a Corresponding probabilistic ICER using 1,000 iterations =€3,158,690/QALY. Figures in the table are rounded, and so calculations may not be directly replicable

Sensitivity analysis

The probability of cost-effectiveness of maralixibat versus SoC was 0% at the €20,000/QALY and €45,000/QALY thresholds for the Applicant and NCPE adjusted base case.

Deterministic one-way sensitivity analysis (DSA) indicated that the most influential parameters in the model for both the Applicant and NCPE adjusted base case related to the annual discount rate for both costs and benefits, the assumption used around weight-based dosing for maralixibat, mortality and the probability of discontinuation of maralixibat.

4. Budget impact of maralixibat

The price-to-wholesaler for one bottle of maralixibat 9.5mg/mL is €30,295 (pack size 30 mL). The estimated total cost per patient per year is dependent on age and weight (due to weight-based dosing). The total cost per patient, per treatment year, based on the average

age of patients in Ireland (eight years) was €298,214 (VAT not applicable).

The Applicant assumed a 100% market share from Year 1 to 5, that use will be restricted to a subpopulation of the licenced population (i.e., those not responding to current SoC) and a start age of 2 months. The Applicant applied the 18-week discontinuation rate calculated from the ICONIC trial for each year. The Applicant's base case assumes 30 patients will be treated in Year 1, which increases to 35 patients by Year 5. The Applicant's estimates the five-year cumulative gross drug-budget impact of maralixibat is approximately €26.9 million. Given that this treatment will not displace treatments the net budget impact is similar.

The NCPE adjusted budget impact model is based on the average age of patients in Ireland (eight years) and applies the updated annual discontinuation rate calculated and applied in the cost-effectiveness model. The NCPE adjusted budget impact estimates the five-year cumulative gross drug-budget impact of maralixibat is approximately €56.7 million.

5. Patient Organisation Submission

A patient organisation submission was received from Irish Liver Network Organisation and has been shared with the HSE. This submission will form part of the information that the HSE considers when making their drug-funding decision.

6. Conclusion

The NCPE recommends that maralixibat (Livmarli®) not be considered for reimbursement, unless cost effectiveness can be improved relative to existing treatments.

Next steps

The NCPE Assessment Report and recommendation, will be considered by the HSE when making their decision on reimbursement, while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

Further information on this process may be found **here.**

Further information on the status of this decision may be found here.