NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Maralixibat for treating progressive familial intrahepatic cholestasis

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of maralixibat within its marketing authorisation for treating progressive familial intrahepatic cholestasis.

Background

Progressive familial intrahepatic cholestasis (PFIC) is the name given to a group of genetic disorders that affect the liver and result in the flow of bile from the liver to the gut being reduced or stopping completely (cholestasis).

Bile is produced by the liver, stored in the gall bladder and then released during digestion. It is used to help the body absorb fats and nutrients and get rid of toxins. Bile acids are then re-absorbed and returned to the liver via the small intestine. When bile flow is reduced or stops completely, it can lead to poor weight gain, slower growth, and an excess of toxins in the body.

Initial symptoms of PFIC include greasy stools or watery diarrhoea, jaundice and itching (pruritus). Untreated it leads to complications including portal hypertension, liver scarring (cirrhosis) and failure, and hepatocellular carcinoma, a type of liver cancer. It can also cause problems outside the liver such as diarrhoea, deafness and pancreatitis.[1,2]

PFIC is inherited in an autosomal recessive pattern,[3] meaning that two copies of the mutated gene (one from each parent) must be present for it to develop. It has been reported that the three main subtypes of the disorder, PFIC type 1, PFIC type 2, and PFIC type 3 are mainly caused by mutations and variations in ATP8B1, ABCB11, and ABCB4 genes respectively.[4] PFIC type 1 and PFIC type 2 onset usually occurs in the first months of life, whereas PFIC type 3 can also appear later in infancy, childhood or even young adulthood.[2]

The exact prevalence of PFIC remains unknown. Estimated prevalence at birth has been reported as varying between 1 per 50,000 and 1 per 100,000; this is likely to be a worldwide estimate but the data on which these rates are based is unclear.[2,5] Approximately 32 children per year may require genetic testing for PFIC in the UK according to estimates from the UK Genetic Testing Network (closed 2018).[3]

PFIC usually progresses to cirrhosis within the first decade of life and is ultimately fatal if untreated.[3] A 2010 multi-centre retrospective study of 145 patients with PFIC with mutations in either ATP8B1 or ABCB11 found that 50% of patients not undergoing surgical diversion or liver transplant survived to the age of 10 but almost none were alive at the age of 20 years.[6] Itching can significantly impact the quality of life of babies and children with PFIC and their carers, often interrupting sleep and contributing to fatigue.

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Current clinical management focuses on relieving symptoms and slowing liver damage. HST17 recommends odevixibat for treating PFIC in people 6 months and older (Odevixibat for treating progressive familial intrahepatic cholestasis). Surgical interventions such as partial external biliary diversion and surgical biliary diversion are also sometimes used. However, liver transplant, requiring lifelong medical follow-up and the use of anti-rejection medications, remains the only definitive treatment for PFIC in some patients. In addition, patients may require additional nutritional support, for example nasogastric feeding.[2,3]

The technology

Maralixibat (Livmarli, Mirum Pharmaceuticals).

Maralixibat does not currently have a marketing authorisation in the UK for PFIC type 2. It is being studied in an open-label trial of children with PFIC types 1-3.

Intervention(s)	Maralixibat
Population(s)	People with progressive familial intrahepatic cholestasis (PFIC)
Subgroups	If the evidence allows the following subgroups will be considered: • PFIC type 1, 2 and 3
Comparators	• odevixibat Established clinical management without odevixibat which may include: • off-label drug treatments such as ursodeoxycholic acid • surgical interventions such as partial external biliary diversion or surgical biliary diversion
Outcomes	The outcome measures to be considered include: • time to liver event (surgery, transplant or liver cancer) • change in serum bile acid level • change in liver enzymes and bilirubin levels • change in symptoms of PFIC including reduction of pruritus • measures of faltering growth • overall survival • number of patients requiring surgical interventions • adverse effects of treatment • health-related quality of life (for patients and carers)

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Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	**Related Technology Appraisals:** Appraisal in development (including suspended appraisals) Odevixibat for treating progressive familial intrahepatic cholestasis Highly specialised technologies guidance HST17. February 2022. Maralixibat for treating cholestatic disease in Alagille Syndrome Proposed NICE technology appraisal ID3941. Publication date to be confirmed. Odevixibat for untreated cholestatic liver disease in Alagille syndrome Proposed NICE technology appraisal TS ID 10643. Publication date to be confirmed. **Related Guidelines:** Faltering growth: recognition and management of faltering growth in children (2017). NICE guideline 75. Review date to be confirmed. **Related Quality Standards:** Liver disease (2017) NICE quality standard 152 **Related NICE Pathways:** Faltering growth (2018) NICE pathway

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Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019). Chapter 69 Liver transplantation service (adults and children), Chapter 110 Specialist gastroenterology, hepatology and nutritional support services for children, Chapter 111. Clinical genomic services (adults and children) Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1, 2, 4 & 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Where do you consider maralixibat will fit into the existing care pathway for progressive familial intrahepatic cholestasis?

Would maralixibat be a candidate for managed access?

Do you consider that the use of maralixibat can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.

Are there any groups of people for whom odevixibat would not be suitable, but for whom maralixibat would be suitable as a treatment for progressive familial intrahepatic cholestasis?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

NICE intends to evaluate this technology through its Single Technology Appraisal process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-tehnology-appraisal-guidance/changes-to-health-technology-evaluation).

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References

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2. Orphanet Progressive familial intrahepatic cholestasis (2009). Accessed January 2023.
3. A4250 for progressive familial intrahepatic cholestasis. NIHR Innovation Observatory Evidence Briefing: September 2017.
4. Zarenezhad M, Dehghani SM, Ejtehadi F, Fattahi MR, Dastsouz H, Fardaei M, Tabei MB (2017) Investigation of common variations of ABCB4, ATP8B1 and ABCB11 genes in patients with progressive familial intrahepatic cholestasis. Hepatitis monthly, 2017, 17(2).
5. Progressive familial intrahepatic cholestasis. Genetics Home Reference (2009). Accessed January 2023.
6. Pawlikowska L, Strautnieks S, Jankowska I, et al. Differences in presentation and progression between severe FIC1 and BSEP deficiencies. Journal of Hepatology. 2010;53(1):170-178.

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