NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Maralixibat for treating type 2 progressive familial intrahepatic cholestasis

Draft scope

Draft remit/evaluation objective

To evaluate the benefits and costs of maralixibat within its marketing authorisation for treating type 2 progressive familial intrahepatic cholestasis (PFIC2) for national commissioning by NHS England.

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 and slower growth, and an excess of toxins in the body.

PFIC is inherited in an autosomal recessive pattern[1], meaning that two copies of the mutated gene (one from each parent) must be present for it to develop. There are three main subtypes of the disorder, PFIC1, PFIC2, and PFIC3[2]. In PFIC2, mutations and variations in the ABCB11 gene cause the bile salt export pump protein to be deficient or completely absent, meaning liver cells have reduced ability to secrete bile[2].

Initial symptoms of PFIC type 2 include 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[,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[3,4.] Of these people, 50-60% will have PFIC2[3]. 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)[5].

PFIC type 2 usually appears in the first few months of life and progresses to cirrhosis within the first decade[3]. It is ultimately fatal if untreated and only 33% of PFIC type 2 children survive to adulthood without a transplant[6]. Itching can have a significant impact on the quality of life of babies and children with PFIC and their carers, often interrupting sleep and contributing to fatigue.

There are currently no licensed therapies for PFIC. Current clinical management focusses on relieving symptoms and slowing liver damage. It often includes initial off-label drug treatment with ursodeoxycholic acid. Common surgical interventions include partial external biliary diversion and internal ileal exclusion. Liver transplant remains the only definitive treatment for some patients with PFIC and requires lifelong medical follow-up and use of anti-rejection medications. In addition, patients may require additional nutritional support, for example nasogastric feeding[2,3]. There is no published NICE guidance for PFIC.

The technology

Maralixibat (LUM001, Mirum Pharmaceuticals) is a selective inhibitor of the apical sodium-dependent bile acid transporter (ASBT). ASBTs help the reabsorption of bile acids through the small intestine. Maralixibat aims to stop the recycling of bile acids to prevent toxic levels accumulating in the liver. It is administered orally as a liquid.

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 type 2
Comparators	Established clinical management without maralixibat which may include: • off-label drug treatments such as ursodeoxycholic acid • surgical interventions such as partial external biliary diversion or internal ileal exclusion
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

	• measures of disease progression • number of patients requiring surgical interventions • adverse effects of treatment • health-related quality of life (for patients and carers)
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options
Clinical Effectiveness	• overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)
Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used
Impact of the technology beyond direct health benefits	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.

Other considerations	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangement for the intervention under evaluation
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Appraisal in development (including suspended appraisals) Odevixibat (A 4250) for progressive familial intrahepatic cholestasis Proposed NICE technology appraisal ID1570. 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
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

What is the prevalence and incidence of PFIC type 2 in England?

Could treatment with maralixibat continue in people aged over 17 years in clinical practice?

Have all relevant comparators for maralixibat been included in the scope?

How effective are surgical interventions at controlling acid accumulation and itch in people with PFIC type 2? Which surgical interventions would be used in NHS clinical practice?

Which treatments are considered to be established clinical practice in the NHS for PFIC type 2? Are the following treatments used in the NHS?

- cholic acid
- chenodeoxycholic acid
- nutraceuticals
- statins
- steroids
- low density lipoprotein apheresis

Is maralixibat likely to be considered a first-line treatment option for PFIC type 2 or would it only be considered after other treatments have failed?

Would maralixibat be used exclusively in the context of a highly specialised service in the NHS?

Are the outcomes listed appropriate?

How is disease progression measured for people with PFIC type 2?

Are there any subgroups of people in whom maralixibat is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider maralixibat will fit into the existing NICE pathway, faltering growth?

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 maralixibat 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 Highly Specialised Technologies Evaluation Committee to identify and consider such impacts.

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of maralixibat can result in any potential significant and 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 Highly Specialised Technologies Evaluation Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to evaluate this technology through its Highly Specialised Technologies Programme. We welcome comments on the appropriateness of evaluating this topic through this process. (Information on the Institute's Highly Specialised Technologies interim methods and evaluation processes is available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf.

References

1. Progressive Familial Intrahepatic Cholestasis Advocacy and Resource Network The disease. Accessed September 2020
2. Baker A, Kerkar N, Todorova L, Kamath BM, Houwen RHJ (2019). Systematic review of progressive familial intrahepatic cholestasis. Clin Res Hepatol Gastroenterol. 2019 Feb;43(1):20-36. doi: 10.1016/j.clinre.2018.07.010.
3. Orphanet Progressive familial intrahepatic cholestasis (2009). Accessed September 2020
4. Genetics Home Reference (2009). Progressive familial intrahepatic cholestasis. Accessed September 2020
5. Odevixibat (A 4250) for progressive familial intrahepatic cholestasis. NICE draft scope. Accessed September 2020.
6. van Wessel DBE, Thompson RJ, Gonzales E, Jankowska I, Sokal E, Grammatikopoulos T, et al (2020). Genotype correlates with the natural

history of severe bile salt export pump deficiency. Journal of Hepatology. 73, 84–93.