NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Maralixibat for treating cholestatic disease in Alagille Syndrome

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of maralixibat within its marketing authorisation for treating cholestatic disease in Alagille Syndrome.

Background

Alagille Syndrome is a genetic disease that can affect multiple organs in the body.[1] It is usually caused by mutations in the JAG1 gene. Around 2% of people with Alagille Syndrome have mutations in the NOTCH2 gene. The mutations can be inherited or occur spontaneously.[1]

Alagille Syndrome can affect the liver, heart, skeleton, eyes, and kidneys. The severity of symptoms varies greatly between individuals.[2] Cholestasis (blockage of the flow of bile from the liver) occurs in most cases, often developing during the first 3 months of life.[3] 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. Therefore, 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, itching, xanthomas (bumps on the skin from fat deposits), increased serum concentration of bile acids and growth failure.[3,4]

The incidence and prevalence of Alagille Syndrome is uncertain because the clinical presentation can be very variable. Incidence is estimated as being from around 1 in 30,000 to 1 in 100,000.[5] This equates to between around 6 and 21 live births in England each year.[6] The incidence may be underestimated because Alagille syndrome may be undiagnosed or misdiagnosed.[1] People with Alagille Syndrome may have only mild symptoms and have a normal life expectancy, but some have severe and even life-threatening complications.[8]

Current treatment for Alagille Syndrome focuses on alleviating symptoms. Treatments to reduce itching may include ursodeoxycholic acid, cholestyramine, rifampicin, naltrexone and antihistamines such as chlorphenamine.[7] Nutritional supplements and high-calorie diets are important for many people with Alagille Syndrome, because of the difficulties cholestasis causes with absorbing fats and nutrients.[2] If Alagille Syndrome does not respond to drug and dietary therapies, a partial biliary diversion may be carried out.[1] For some people, liver function improves over time, but about 15% of people with Alagille Syndrome may eventually need a liver transplant.[2] Currently there is no way to predict whether liver disease in infancy will resolve or progress.[7]

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 treating cholestatic disease in Alagille Syndrome. It has been studied in clinical trials in people aged 12 months to 18 years with Alagille Syndrome, cholestasis and severe pruritus.

Intervention(s)	Maralixibat
Population(s)	People with cholestatic disease related to Alagille Syndrome
Comparators	Established clinical management without maralixibat, which may include: • off-label drug treatments such as ursodeoxycholic acid • dietary changes • surgical interventions such as partial 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 cholestasis including reduction of pruritis • measures of faltering growth • overall survival • number of patients requiring surgical interventions • adverse effects of treatment • health-related quality of life.
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. 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.

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 and NICE Pathways	Maralixibat for treating type 2 progressive familial intrahepatic cholestasis. Highly specialised technologies guidance [ID3818]. Publication date to be confirmed.
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) Sections 110 and 131 Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1 and 2. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Is the population defined appropriately in the scope?

What is the incidence and prevalence of Alagille Syndrome in England? How many people are living with Alagille Syndrome in England?

How is Alagille syndrome diagnosed in the NHS? Is genetic testing carried out and routine for diagnosis of Alagille Syndrome in the NHS?

Is there an under-diagnosis of Alagille syndrome in England given the clinical diversity and multiple manifestations related to the condition?

What proportion of people with Alagille Syndrome have chronic and severely disabling disease?

Could treatment with maralixibat continue in people aged over 18 years in the NHS?

Which treatments are considered to be established clinical practice in the NHS for cholestatic disease in Alagille Syndrome? Have all relevant comparators for maralixibat been included in the scope?

How are the services for cholestatic disease in Alagille Syndrome, including the diagnosis and management of the condition, delivered in the NHS?

Are the outcomes listed appropriate? Are there other outcomes that should be listed?

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?

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 committee to identify and consider such impacts.

Do you consider maralixibat 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 Appraisal 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 appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1 National Organization for Rare Disorders. Alagille Syndrome. Available at https://rarediseases.org/rare-diseases/alagille-syndrome/. Accessed September 2021.

2 Genetic and Rare Diseases Information Center. Alagille Syndrome. Available at https://rarediseases.info.nih.gov/diseases/804/alagille-syndrome. Accessed September 2021.

3 Turnpenny P, Ellard S. (2012) Alagille syndrome: pathogenesis, diagnosis and management. Eur J Hum Genet 20: 251–257. https://doi.org/10.1038/ejhg.2011.181

4 Spinner NB, Gilbert MA, Loomes KM, et al. Alagille Syndrome. 2000 May 19 [Updated 2019 Dec 12]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.

5 Diaz-Frias J, Kondamudi NP. Alagille Syndrome. [Updated 2021 Jun 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available at: https://www.ncbi.nlm.nih.gov/books/NBK507827.

6 Office for National Statistics (2020) Births in England and Wales: summary tables. Available at https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/datasets/birthsummarytables. Accessed September 2021.

7 Children's Liver Disease Foundation. Alagille Syndrome. Available at https://childliverdisease.org/liver-information/childhood-liver-conditions/alagille-syndrome/ Accessed September 2021.

8 National Institute of Diabetes and Digestive and Kidney Diseases. Definition & Facts for Alagille Syndrome. Available at https://www.niddk.nih.gov/health-information/liver-disease/alagille-syndrome/definition-facts. Accessed September 2021.