NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Maralixibat for treating cholestatic pruritus in Alagille Syndrome

Final scope

Final remit/evaluation objective

To appraise the clinical and cost effectiveness of maralixibat within its marketing authorisation for treating cholestatic pruritus 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, kidneys and vascular system.[2] The severity of symptoms varies greatly between individuals.[3] Cholestasis (impairment of bile flow due to bile duct paucity) occurs in most cases, often developing during the first 3 months of life.[4] 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 fat-soluble vitamins 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, pruritus (itching), xanthomas (bumps on the skin from fat deposits), increased serum concentration of bile acids and growth failure.[4,5] 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 about 80% of cases at 2 years.[6]

The incidence of Alagille Syndrome at birth is reported in the literature to range from 1 in 30,000 to 1 in 70,000.[7] This is because of the variable clinical presentations of the condition and because its diagnostic criteria have evolved over the years.[8] When Alagille syndrome was first recognised in the 1970s, it was defined as bile duct paucity associated with at least 3 of 5 major criteria (cholestasis, heart disease, vertebral anomalies, eye problems) and treated as a liver condition.[4] The condition is treated as a multi-system disorder today. With an understanding that not all patients with the disorder will have hepatic abnormalities in the neonatal period, and with the revised diagnostic criteria requiring fewer positive findings from an expanded range of characteristics especially in people with a positive family history,[8,9] most recently it has been reported that the true incidence is likely to be around 1 in 30,000.[2,9,10] People with Alagille Syndrome may have only mild symptoms and have a normal life expectancy, but some have severe and even life-threatening complications.[11]

Current treatment for Alagille Syndrome focuses on alleviating symptoms. Treatments to reduce itching may include ursodeoxycholic acid, cholestyramine, rifampicin, naltrexone, ondansetron, selective serotonin reuptake inhibitors (SSRIs). Antihistamines such as chlorphenamine may be used to aid sleep.[12] 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.[11] If Alagille Syndrome does not respond to drug and dietary therapies, a partial biliary diversion may be carried out although this is rare in the UK.[4] For some people, symptoms may improve over time[3], but between 15% and 50% of people with Alagille Syndrome will have a liver transplant before 18 years of age.[6,10] Currently there is no way to predict whether liver symptoms in infancy will resolve or progress.[5]

The technology

Maralixibat (LUM001, Mirum Pharmaceuticals) has a marketing authorisation for the treatment of cholestatic pruritus in patients with Alagille Syndrome 2 months of age and older.

Intervention(s)	Maralixibat (in addition to established clinical management)
Population(s)	People with cholestatic pruritus related to Alagille Syndrome

Comparators	• Established clinical management without maralixibat, which may include:
	  ○ off-label drug treatments such as ursodeoxycholic acid, cholestyramine, rifampicin, ondansetron, naltrexone, SSRIs and antihistamines
	  ○ dietary changes
	  ○ surgical interventions such as liver transplantation

Outcomes	The outcome measures to be considered include: • change in symptoms of cholestasis including pruritus • change in serum bile acid level • change in xanthomas • change in sleep disturbance • change in liver enzymes and bilirubin levels • time to liver event (surgery, transplant or liver cancer) • measures of faltering growth and failure to thrive • transplant-free survival • number of patients requiring surgical interventions • overall survival • adverse effects of treatment • health-related quality of life (patient and carer-reported).

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. 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 in development:** Maralixibat for treating progressive familial intrahepatic cholestasis [ID3818] Publication date to be confirmed Odevixibat for treating cholestatic pruritus in Alagille Syndrome. NICE technology appraisal guidance [ID6181] Publication date to be confirmed
Related National Policy	The NHS Long Term Plan (2019) NHS Long Term Plan NHS England (2018) NHS manual for prescribed specialist services (2018/2019) NHS England (2018) Manual for prescribed specialised services 2018/19 section 110 Specialist gastroenterology, hepatology and nutritional support services for children, and 131 Specialist services for complex liver, biliary and pancreatic diseases in adults.

References

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3 Genetic and Rare Diseases Information Center. Alagille Syndrome. Available at https://rarediseases.info.nih.gov/diseases/804/alagille-syndrome. Accessed January 2023.

4 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

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9 Ayoub MD, Kamath BM. Diagnostics (Basel). 2020; 10(11): 907. Alagille Syndrome: Diagnostic Challenges and Advances in Management - PMC (nih.gov)

10 Vandriel SM, Li L, She H, et al. (2023) Natural history of liver disease in a large international cohort of children with Alagille syndrome: Results from the GALA study. Hepatology 77, 512–529. https://doi.org/10.1002/hep.32761

11 National Institute of Diabetes and Digestive and Kidney Diseases. Definition & Facts for Alagille Syndrome. Available at Definition & Facts for Alagille Syndrome | NIDDK (nih.gov). Accessed January 2023.

12 Children's Liver Disease Foundation. Alagille Syndrome. Available at https://childliverdisease.org/liver-information/childhood-liver-conditions/alagille-syndrome/ Accessed January 2023.