NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Odevixibat for treating cholestasis and pruritus in Alagille Syndrome

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of odevixibat within its marketing authorisation for treating cholestasis and 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, and kidneys. The severity of symptoms varies greatly between individuals.[2] Cholestasis (impairment of bile flow due to bile duct paucity) 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 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, xanthomas (bumps on the skin from fat deposits), increased serum concentration of bile acids and growth failure.[3,4] Pruritus (itching) 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.[5]

The incidence and prevalence of Alagille Syndrome is uncertain because the clinical presentation can be very variable. Incidence at birth is estimated to be around 1 in 30,000 to 1 in 70,000 live births.[6] This equates to between around 9 and 21 live births in England each year.[7] The incidence may be underestimated because Alagille Syndrome may be undiagnosed or misdiagnosed,[5,6] and an incidence estimate of 1 in 30,000 to 1 in 50,000 is also reported.[6] 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, ondansetron, selective serotonin reuptake inhibitors (SSRIs). Antihistamines such as chlorphenamine may be used to aid sleep.[9] 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.[8] If Alagille Syndrome does not respond to drug and dietary therapies, a partial biliary diversion may be carried out although this is relatively uncommon in the UK.[3] For some people, symptoms may improve over time[2], but between 15% and 47% of people with Alagille Syndrome will have a liver transplant before 18 years of age.[5] For people with Alagille Syndrome and neonatal cholestasis, almost 60% of

patients will have a liver transplant before 18 years of age[10]. Currently there is no way to predict whether liver symptoms in infancy will resolve or progress.[4]

The technology

Odevixibat (Bylvay, Albireo Pharma) does not currently have a marketing authorisation in the UK for treating cholestasis and pruritus in Alagille Syndrome. It has been studied in clinical trials in people with Alagille Syndrome. It has a marketing authorisation in the UK for treating progressive familial intrahepatic cholestasis (PFIC) in people aged 6 months or older.

Intervention(s)	Odevixibat
Population(s)	People with cholestasis and pruritis related to Alagille Syndrome

Comparators	• Established clinical management without odevixibat, 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 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 highly specialised technology appraisals:** Odevixibat for treating progressive familial intrahepatic cholestasis (2022) NICE highly specialised technology guidance HST17. **Related technology appraisals in development:** Maralixibat for treating cholestatic pruritus in Alagille Syndrome. NICE technology appraisal guidance [ID3941] Publication date to be confirmed Odevixibat for treating cholestasis and pruritus in Alagille Syndrome. NICE technology appraisal guidance [ID6181] (this evaluation).
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.

Questions for consultation

Population:

- Is the population defined appropriately in the scope?

Incidence and prevalence of Alagille Syndrome:

- How many people are born with Alagille Syndrome in England each year?

- There is a range of incidence estimates for Alagille Syndrome reported in the literature, which estimate reflects the incidence of Alagille Syndrome in England more closely?

Neonatal cholestasis related to Alagille Syndrome

- Among people with Alagille Syndrome in England, how many of them present with neonatal cholestasis, and how many of them present with non-neonatal cholestasis?

- Among people with neonatal or non-neonatal cholestasis related to Alagille Syndrome in England, how many of them would have had a liver transplant by age 18, respectively?

Cholestasis and pruritus related to Alagille Syndrome

- Odevixibat is anticipated to be indicated for treating cholestasis and pruritus in patients with Alagille syndrome, how many people with Alagille Syndrome are living with cholestasis and pruritus in England?

- If recommended, would all patients with Alagille Syndrome and cholestasis and pruritus be eligible for odevixibat?

- Among people with cholestasis and pruritus related to Alagille Syndrome in England, how many of them would have had a liver transplant by age 18?

Treatment pathway and comparator

- Where do you consider odevixibat will fit into the existing care pathway for cholestasis and pruritus related to Alagille Syndrome?

- If recommended, would odevixibat replace liver transplant in the NHS? If odevixibat is not going to completely remove the need for liver transplant, how many patients with cholestasis and pruritus and Alagille Syndrome would still need liver transplant in the NHS?

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

Would odevixibat be a candidate for managed access?

Which treatments are considered to be established clinical practice in the NHS for cholestasis and pruritus in Alagille Syndrome? Have all relevant comparators for odevixibat been included in the scope?

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

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

Do you consider that the use of odevixibat 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.

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 odevixibat 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).

References

1 National Organization for Rare Disorders. Alagille Syndrome. Available at https://rarediseases.org/rare-diseases/alagille-syndrome/. Accessed January 2023.

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

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 Kamath, B.M. et al. (2018) 'Systematic Review: The Epidemiology, Natural History, and Burden of Alagille Syndrome', Journal of Pediatric Gastroenterology and Nutrition, 67(2), pp. 148–156. doi:10.1097/MPG.0000000000001958.

6 Leonard, L.D. *et al.* (2014) 'Clinical utility gene card for: Alagille Syndrome (ALGS)', *European Journal of Human Genetics*, 22(3).

7 Office for National Statistics (2021) Births in England and Wales: summary tables. Available at https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/datasets/birthsummarytables. Accessed January 2023.

8 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.

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

10 Vandriel S, Liting L et al. (2020). Clinical Features and Natural History of 1154 Alagille Syndrome Patients: Results from the International Multicenter GALA Study Group. doi:10.1016/S0168-8278(20)31582-8. Accessed January 2023.