NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Odevixibat (A 4250) for progressive familial intrahepatic cholestasis

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of Odevixibat (A 4250) 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 and 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 subtypes of the disorder, PFIC1, PFIC2, and PFIC3 are mainly caused by mutations and variations in ATP8B1, ABCB11, and ABCB4 genes respectively[4]. PFIC1 and PFIC2 onset usually occurs in the first months of life, whereas PFIC3 can also appear later in infancy, in childhood or even during 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 rate are based is unclear[2, 5, 6]. 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 PIFC 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[7]. 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 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].

The technology

Odevixibat (A 4250) (brand name unknown, Abireo) is a selective inhibitor of ileal bile acid transporters (IBATs). IBATs help the reabsorption of bile acids through the small intestine. Odevixibat (A 4250) aims to stop the recycling of bile acids to prevent toxic levels accumulating in the liver. Odevixibat (A 4250) is administered orally as a capsule.

Odevixibat (A 4250) does not currently have a marketing authorisation in the UK for PFIC. It is being studied in a double-blind, randomised, placebo-controlled trial of children with PFIC types 1 and 2.

Intervention(s)	Odevixibat (A 4250)
Population(s)	People with progressive familial intrahepatic cholestasis
Comparators	Established clinical management without Odevixibat (A 4250) which may include: • off-label drug treatments such as ursodeoxycholic acid • surgical interventions such as partial external biliary diversion or internal ileal exclusion • liver transplant

Outcomes	The outcome measures to be considered include: • change in serum bile acid level • change in symptoms of PFIC including reduction 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)
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. The availability of any managed access arrangement for the intervention 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 and NICE Pathways	Related Guidelines: 'Faltering growth: recognition and management of faltering growth in children' (2017). NICE guideline 75 Review date to be confirmed. 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 in England?

Which treatments are established clinical practice in the NHS for PFIC?

Is Odevixibat (A 4250) likely to be considered a first-line treatment option for PFIC or would it only be considered after other treatments have failed?

Do the comparators currently listed in the draft scope reflect the treatments that are already in use in the NHS that will potentially be displaced by the uptake of Odevixibat (A 4250)?

At what stage in the current pathway is liver transplant likely to be offered as a treatment for PFIC?

Are the outcomes listed appropriate? Specifically,

- is change in serum bile acid level a clinically meaningful outcome?
- is Odevixibat (A 4250) expected to have any clinical benefit in terms of the number of patients experiencing disease progression or requiring liver transplant?
- is Odevixibat (A 4250) expected to have any positive or negative impact on growth?

Are patients with type 3 PFIC, (that is, those with PFIC that is linked to ABCB4 gene mutations/variations) likely to be eligible for treatment with Odevixibat (A 4250)?

Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, 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 Odevixibat (A 4250) 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.

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)?

References

1 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.

2 Orphanet Progressive familial intrahepatic cholestasis (2009). Accessed 10 March 2020

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 Albireo Enrolls First Patient in Phase 3 PFIC Trial of A4250. Albireo press release (2018). Accessed 08 April 2020

6 Progressive familial intrahepatic cholestasis. Genetics Home Reference (2009). Accessed 08 April 2020

7 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.

