**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Proposed Health Technology Appraisal**

# Obeticholic acid for treating liver fibrosis in people with non-alcoholic steatohepatitis

**Draft scope (pre-referral)**

## Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of obeticholic acid within its marketing authorisation for treating liver fibrosis in people with non-alcoholic steatohepatitis.

## Background

Non-alcoholic fatty liver disease (NAFLD) is an excess of fat in the liver (hepatic steatosis) that is not a result of excessive alcohol consumption but other causes. These can include side effects of certain medications, hepatitis C virus infection and particular endocrine conditions. NAFLD progresses from hepatic steatosis to inflammatory non-alcoholic steatohepatitis (NASH), potentially resulting in fibrosis or cirrhosis. Fibrosis is where persistent inflammation causes scar tissue around the liver and nearby blood vessels, but the liver is still able to function normally. Cirrhosis is where the liver shrinks and becomes scarred and lumpy; this damage is permanent and can lead to liver failure (where your liver stops working properly) and liver cancer. NAFLD is largely asymptomatic in the early stages. Occasionally, people with NASH or fibrosis may experience dull or aching pain over the ribs, fatigue, unexplained weight loss, and weakness[1]. A proportion of people will develop liver failure or hepatocellular carcinoma, and some will need a liver transplant.

The true prevalence of NASH is uncertain because many people are asymptomatic. It is estimated that approximately 20–33% of the UK population is in the early stages of NAFLD, and up to 5% has NASH[1,2]. It is estimated that 25–40% of people with NASH will develop progressive liver fibrosis, 20–30% of whom will ultimately progress to cirrhosis[3]. The average age of people with NASH is 40–50 years, and for NASH-cirrhosis it is 50–60 years. There is a higher risk of developing the condition in people of Hispanic or Asian family origin and a lower risk in people of African family origin.

Current treatment for NASH includes lifestyle modification interventions, with a focus on healthy eating, weight loss and regular exercise[4]. In hospital or specialist care centre settings, treatment with pioglitazone or vitamin E may be considered for adults with advanced liver fibrosis, although neither has UK approval for treating this disease. There are currently no pharmalogical therapies approved for the treatment of NASH in the UK.

## The technology

Obeticholic acid (brand name unknown, Intercept Pharmaceuticals) is a selective agonist for the farensoid X receptor (FXR), a nuclear receptor expressed at high levels in the liver and intestine. FXR regulates target genes involved in the control of bile acid synthesis & transport, lipid metabolism & glucose homeostasis. Activation of this receptor decreases the concentrations of bile acids in liver cells. It is given orally as a tablet.


 

Obeticholic acid does not currently have a marketing authorisation in the UK for the treatment of liver fibrosis in adults with NASH. It is being studied in clinical trials compared with placebo in adults with NASH and fibrosis (F2 or F3), and in adults with NASH and advanced fibrosis (F4).

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| **Intervention(s)** | Obeticholic acid |
| **Population(s)** | Adults with non-alcoholic steatohepatitis (NASH) and liver fibrosis |
| **Comparators** | Established clinical management for treating fibrosis in people with NASH, which may include lifestyle modification interventions (such as advice on healthy diet, weight loss when required, and regular exercise).<br><br>For people receiving treatment in secondary or tertiary care, established clinical management may include:<br>• Pioglitazone (does not currently have a marketing authorisation in the UK for this indication)<br>• vitamin E. (does not currently have a marketing authorisation in the UK for this indication) |
| **Outcomes** | The outcome measures to be considered include:<br>• change in fibrosis score<br>• change in Model for End-Stage Liver Disease (MELD) score<br>• liver decompensation event<br>• hepatocellular carcinoma<br>• liver transplantation<br>• progression to cirrhosis<br>• hepatic-related morbidity<br>• hepatic-related mortality<br>• overall survival<br>• event-free survival<br>• duration of hospitalisation<br>• adverse effects of treatment<br>• 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.<br><br>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. |


 

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| | Costs will be considered from an NHS and Personal Social Services perspective.<br><br>The use of obeticholic acid is expected to be conditional on the presence of liver fibrosis. The economic analysis should include the costs associated with diagnostic testing for liver fibrosis in people with non-alcoholic steatohepatitis who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals'. |
| **Other considerations** | If the evidence allows, the following subgroups will be considered:<br>• people with liver fibrosis stage F2 or F3<br>• people with liver fibrosis stage F4 (advanced fibrosis).<br><br>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:**<br><br>Non-alcoholic fatty liver disease (NAFLD): assessment and management (2016) NICE guideline 49. No review date.<br><br>Cirrhosis in over 16s: assessment and management (2016) NICE guideline 50. No review date.<br><br>**Related Quality Standards:**<br><br>Liver disease (2017) NICE quality standard 152<br><br>**Related NICE Pathways:**<br><br>Non-alcoholic fatty liver disease (2017) NICE pathway<br><br>Liver conditions (2017) NICE pathway<br><br>Cirrhosis (2017) NICE pathway |
| **Related National Policy** | The NHS Long Term Plan, 2019. NHS Long Term Plan<br><br>NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019):<br><br>Chapter 69 Liver transplantation service (adults and children)<br><br>Chapter 131 Specialist services for complex liver, biliary and pancreatic diseases in adults.<br><br>Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domain 1. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017<br><br>NHS England (2018) Highly specialised services 2017<br><br>NHS England (2013) Clinical Commissioning Policy: Complex |


 

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| | and Specialised Obesity Surgery. Reference NHSCB/A05/P/a<br>NHS England. 2013/14 NHS Standard Contract for Hepatobiliary and Pancreas (Adult). A02/S/a.<br>NHS England. 2013/14 NHS Standard Contract for Live Liver Transplantation Services (All Ages). A02/S(HSS)/a |

**Questions for consultation**

How many people would you anticipate being eligible for obeticholic acid (i.e. with NASH and liver fibrosis)? What proportion of the total number of people with have NASH in the UK is expected to be undiagnosed?

Have all relevant comparators for obeticholic acid been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for liver fibrosis in people with NASH?

How would people who you would antitcipate to be eligible for obeticholic acid in the NHS be identified?

Are the outcomes listed appropriate?

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

Where do you consider obeticholic acid will fit into the existing NICE pathway, Non-alcoholic fatty liver disease (2017)? In what setting is it most likely to be used?

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 obeticholic acid 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 obeticholic acid 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 obeticholic acid 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] NHS conditions: Non-alcoholic fatty liver disease (NAFLD) https://www.nhs.uk/conditions/non-alcoholic-fatty-liver-disease (accessed November 2019)

[2] British Liver Trust. Non-Alcohol Related Fatty Liver Disease. https://www.britishlivertrust.org.uk/liver-information/liver-conditions/non-alcohol-related-fatty-liver-disease/ (accessed November 2019)

[3] Dyson JK, Anstee QM, McPherson S. (2014) Non-alcoholic fatty liver disease: a practical approach to diagnosis and staging. Frontline Gastroenterology. 5(3):211-218.

[4] Brent A. Neuschwander-Tetri (2017) Non-alcoholic fatty liver disease. BMC Medicine 15:45


 