NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Resmetirom and semaglutide for treating metabolic dysfunction-associated steatohepatitis with liver fibrosis ID6458

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of resmetirom and semaglutide within its marketing authorisation for treating liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis (MASH).

Background

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a chronic disease caused by excess fat in the liver (hepatic steatosis). MASLD is the new name for non-alcoholic fatty liver disease (NAFLD), as agreed by experts internationally in 2023.[1] Using MASLD is preferred because it is more specific about the main associated risk factors of excess weight and metabolic diseases. MASLD is usually seen in people with type 2 diabetes, obesity or other cardiometabolic risk factors such as raised blood pressure or high levels of cholesterol or triglycerides in the blood.[2] MASLD includes a group of conditions of increasing severity[1,2]:

- Isolated fatty liver (fibrosis stage 0), where there is a reversible build-up of fat in the liver but without damage or scarring. This is also called metabolic dysfunction-associated steatotic liver (MASL).

- Metabolic dysfunction-associated steatohepatitis or MASH (fibrosis stage 0 or 1), where there are distinct changes in tissues of the liver (hepatocellular ballooning and lobular inflammation) but no or very little scarring and it can be reversed. MASH in the new name for non-alcohol related steatohepatitis (NASH).

- Fibrosis, moderate or advanced (stage 2 or 3), where persistent inflammation causes scar tissue around the liver and nearby blood vessels, but the liver is still able to function normally.

- Cirrhosis (fibrosis stage 4), where the liver shrinks and becomes heavily scarred and lumpy. This damage is permanent and can lead to liver failure (where the liver stops working properly) and liver cancer.

In the early stages of MASLD there are not usually any symptoms. Occasionally, people with MASH or fibrosis may experience dull or aching pain over the ribs on the lower right side, fatigue, unexplained weight loss, and weakness. Symptoms of cirrhosis are more severe and include yellowing of the skin and eyes (jaundice), itchy skin, and swelling in the legs, ankles, feet or abdomen.

MASLD is estimated to affect up to 1 in 5 people in the UK.[2] Rates are increasing with rising levels of obesity. Global estimates suggest that around 10 to 30% of people with isolated fatty liver progress to steatohepatitis (seen in MASH) and advanced liver disease, but the risk is much higher in the presence of type 2 diabetes

where up to 65% of people have steatosis (fatty liver).[1] People with MASH have a higher rate of liver-related and cardiovascular mortality than the general population.[1]

Treatment of MASLD aims to stop the disease getting worse and help the liver repair as much of the damage as possible. For earlier stage disease including MASH with mild fibrosis, care is usually managed by GPs.[2] Treatment focuses on lifestyle modification interventions, including healthy eating, weight loss and regular exercise. There are currently no medicines approved for MASLD or MASH in the UK. Medicines for associated conditions such as high blood pressure, high cholesterol, type 2 diabetes and obesity may be offered. For later stage MASLD including MASH with moderate or severe fibrosis, care is usually managed in a hospital or specialist care setting.[2] NICE guideline 49 (NG49) recommends that pharmacological treatment with pioglitazone or vitamin E may be considered for adults with NAFLD and advanced liver fibrosis in secondary care settings, typically after and alongside lifestyle modification interventions. However, neither is widely used nor has UK marketing authorisation for treating MASLD. NG49 is currently under review. People with cirrhosis who develop liver failure may be considered for a liver transplant.

The technologies

Resmetirom (brand name unknown, Madrigal Pharmaceuticals) does not currently have a marketing authorisation in the UK for treating liver fibrosis (without cirrhosis) caused by MASH. It has been studied in a clinical trial compared with placebo in adults with NASH and liver fibrosis.

Semaglutide (brand name unknown, Novo Nordisk Ltd) does not currently have a marketing authorisation in the UK for treating liver fibrosis (without cirrhosis) caused by MASH. It has been studied in clinical trials comparing against placebo in adults with non-cirrhotic MASH and with stage 2 or 3 fibrosis.

Interventions	• Resmetirom • Semaglutide The interventions are monotherapies in addition to established clinical management
Population(s)	Adults with significant liver fibrosis caused by metabolic dysfunction-associated steatohepatitis (MASH)
Subgroups	If the evidence allows, subgroups by liver fibrosis stage will be considered
Comparators	• Established clinical management, which may include lifestyle modification interventions (such as advice on healthy diet, weight loss when required, and regular exercise), unlicensed use of pioglitazone and vitamin E • The interventions will be compared to each other

Outcomes	The outcome measures to be considered include: • change in NASH (or MASH) markers • change in NAFLD (or MASLD) activity score • change in fibrosis stage • liver transplantation • hepatocellular carcinoma • overall survival • 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. 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:** Semaglutide for treating non-alcoholic steatohepatitis with significant liver fibrosis. NICE technology appraisal guidance [ID6458] Publication date to be confirmed. Obeticholic acid for treating liver fibrosis in people with steatohepatitis. NICE technology appraisal guidance [ID1645] Publication date to be confirmed. Semaglutide for managing overweight and obesity and the reduction of associated cardiovascular risk. [ID6441] (including a review of TA875 and TA910) **Related NICE guidelines:** Cirrhosis in over 16s: assessment and management (2016) NICE guideline NG50.

	Related NICE guidelines in development: Non-alcoholic fatty liver disease (NAFLD): assessment and management (2016) NICE guideline NG49. Update in progress. Publication date to be confirmed **Related health technologies guidance:** MRI-based technologies for assessing non-alcoholic fatty liver disease (2023) NICE diagnostics guidance 50. FibroScan for assessing liver fibrosis and cirrhosis outside secondary and specialist care. (2023) NICE diagnostics guidance 48. LIVERFASt for assessing and monitoring liver fibrosis, activity and steatosis (2023) NICE MedTech innovation briefing 317. **Related quality standards:** Liver disease (2017) NICE quality standard 152.

Questions for consultation

Which treatments are considered to be established clinical practice in the NHS for liver fibrosis caused by metabolic dysfunction-associated steatohepatitis (MASH)?

How are people with liver fibrosis caused by MASH who might be eligible for treatment with the technologies identified in NHS practice?

How is the disease activity of metabolic dysfunction-associated steatotic liver disease (MASLD) and MASH routinely assessed in the NHS? Which scales are used in clinical practice in the NHS to stage liver fibrosis?

Have all relevant comparators for the technologies been included in the scope?

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

Are the outcomes listed appropriate?

Where do you consider the technologies will fit into the existing care pathway for liver fibrosis caused by MASH?

Please select from the following, will the technologies be:
A. Prescribed in primary care with routine follow-up in primary care
B. Prescribed in secondary care with routine follow-up in primary care
C. Prescribed in secondary care with routine follow-up in secondary care
D. Other (please give details):
For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.

Would the technologies be candidates for managed access?

Do you consider that the use of the technologies 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.

Please indicate if any of the treatments in the scope, including pioglitazone, are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics.

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 the technologies 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 appraise this technology through its Multiple Technology Appraisal (MTA) process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on NICE's health technology evaluation processes is available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).

References

1. EASL-EASD-EASO. (2024) Clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol 81:492-542.

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 March 2025)