NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Semaglutide for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6458]

Final scope

Final remit/evaluation objective

To appraise the clinical and cost effectiveness of semaglutide within its marketing authorisation for treating moderate to advanced 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] MASLD is preferred to NAFLD 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.

- 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).

- MASH with moderate or advanced (stage 2 or 3) fibrosis, 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.

Within the spectrum of MASLD, MASH has complex interrelationships with multiple metabolic disorders, including type 2 diabetes, obesity, cardiovascular disease and chronic kidney disease.[3] With MASH, insulin resistance becomes more pronounced, and fat accumulation in the liver further impairs insulin signalling, reinforcing the cycle of insulin resistance. The liver's role as a central metabolic hub means that MASH can significantly impact whole-body metabolism and contribute to liver-related and cardiovascular complications.

There are often no specific symptoms of MASLD, even in the later stages of the disease. Occasionally, people may experience tiredness or fatigue, or a dull ache

over the ribs on the lower right side.[2] Cirrhosis may also be asymptomatic, although as the liver becomes decompensated, symptoms may include yellowing of the skin and eyes (jaundice), itching, and swelling in the legs, ankles, feet or abdomen (ascites). In NHS practice, people with liver fibrosis caused by MASLD are typically identified in primary care incidentally, by elevated liver enzymes in blood tests or by steatosis being observed on ultrasound imaging.

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 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] Rates of premature death from MASLD are higher for people living in more deprived areas of England.[4]

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. Bariatric surgery to promote weight loss and improve MASH may be suitable for a small proportion of patients. 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 MASLD 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 technology

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 metabolic dysfunction-associated steatohepatitis (MASH). It has been studied in clinical trials comparing against placebo in adults with non-cirrhotic MASH and with stage 2 or 3 fibrosis.

Intervention	Semaglutide in addition to established clinical management
Population	Adults with non-cirrhotic moderate to advanced liver fibrosis (consistent with stage 2 or 3) caused by metabolic dysfunction-associated steatohepatitis (MASH)
Subgroups	If the evidence allows the following subgroups will be considered: • subgroups by liver fibrosis stage • subgroups by BMI level • people with type 2 diabetes

Comparators	Established clinical management without semaglutide, 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 • Resmetirom (subject to a NICE evaluation).
Outcomes	The outcome measures to be considered include: • resolution of MASH • change in fibrosis stage • progression to cirrhosis • occurrence of hepatic decompensation events, including development of ascites, hepatic encephalopathy, variceal bleeding • liver transplantation • hepatocellular carcinoma • Change in weight from baseline • Change in HbA1c from baseline • Changes in cardiovascular disease risk factors e.g. HDL, LDL and SBP • 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. NICE's Health Technology Assessment Innovation Laboratory (HTA Lab) has published a report on evaluating MASH treatments. This provides NICE's expectations and specifications for the economic model concept (section 8).

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:** Semaglutide for managing overweight and obesity (2023) NICE technology appraisal guidance 875 **Related technology appraisals in development:** Obeticholic acid for treating liver fibrosis in people with steatohepatitis. [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) Resmetirom for treating non-alcoholic steatohepatitis and liver fibrosis. [ID6529] Publication date to be confirmed **Related NICE guidelines:** Non-alcoholic fatty liver disease (NAFLD): assessment and management (2016) NICE guideline NG49. Update in progress. Publication date to be confirmed Cirrhosis in over 16s: assessment and management (2016) NICE guideline NG50. FibroScan for assessing liver fibrosis and cirrhosis outside secondary and specialist care. (2023) NICE diagnostics guidance 48 MRI-based technologies for assessing non-alcoholic fatty liver disease. (2023) NICE diagnostics guidance 50 **Related quality standards:** Liver disease (2017) NICE quality standard 152

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)

3. NICE. Evaluating metabolic dysfunction-associated steatohepatitis (MASH) treatments. HTA Innovation Laboratory Report, June 2025 (accessed June 2025)

4. Office for Health Improvement & Disparities. Liver disease profile, December 2024 update (accessed June 2025)