NIHR | Innovation Observatory

Newcastle University

# Health Technology Briefing
# September 2022

# Semaglutide for treating peripheral arterial disease (PAD) and type 2 diabetes

| Company/Developer | Novo Nordisk Ltd |
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☐ New Active Substance ☒ Significant Licence Extension (SLE)

| NIHRIO ID: 30536 | NICE TSID: 11791 | UKPS ID: N/A |
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## Licensing and Market Availability Plans

Currently in phase III clinical trials.

## Summary

Semaglutide is in clinical development for the treatment of type 2 diabetes and peripheral arterial disease (PAD). Diabetes mellitus is a condition where blood glucose levels are too high due to an issue with either insulin production (type 1) or insulin resistance (type 2). Over time, people who have diabetes and high blood sugar can develop serious life-threatening diseases, including heart diseases such as PAD. PAD is a common condition where a build-up of fatty deposits in the arteries restricts blood supply to arm or leg muscles. Symptoms often include mild to severe pain in the arms or legs affected. There are not currently any drugs recommended to treat patients with PAD and type 2 diabetes.

Semaglutide is a medicinal product that acts in the same way as glucagon-like peptide-1 (GLP-1) which is a natural hormone in the body. Semaglutide regulates blood sugar levels by increasing insulin production when blood sugar levels are high. Additionally, GLP-1 has other effects that are potentially promising therapeutic benefits from a cardiovascular risk perspective. If licensed, semaglutide administered vis subcutaneous injection would provide a novel treatment option for adults with type 2 diabetes and PAD.

## Proposed Indication

Patients with type 2 diabetes and Peripheral Arterial Disease (PAD).[1]

## Technology

### Description

Semaglutide (Ozempic) acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. GLP-1 is a physiological hormone that has multiple actions in glucose and appetite regulation, and in the cardiovascular system. Semaglutide reduces blood glucose in a glucose dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. Semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite. In addition, semaglutide reduces the preference for high fat foods.[2]

Semaglutide is currently in clinical development for the treatment of adult patients with type 2 diabetes and PAD. In the phase III clinical trial (STRIDE, NCT04560998) participants will receive semaglutide subcutaneous (SC) injection(s) once-weekly for 52 weeks, with dose escalating from 0.25 mg to 1.0 mg.[1]

### Key Innovation

Type 2 diabetes (T2D) is one of the leading causes of PAD; ~30% of patients with PAD have T2D. While anti-atherosclerotic drugs and lifestyle changes are recommended, there are no effective drugs to specifically improve functional outcomes in PAD and T2D.[3] If licensed, semaglutide would be a novel treatment option for adult patients with T2D and PAD.

### Regulatory & Development Status

Semaglutide currently has Marketing Authorisation in the UK for the following indications:[2,4,5]

- as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of: ≥30 kg/m2 (obesity), or ≥27 kg/m2 to <30 kg/m2 (overweight) in the presence of at least one weight-related comorbidity
- as monotherapy or in combination, for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise

Semaglutide is currently in phase III clinical trials for several indications, some of which include:[6]

- Major adverse cardiovascular events, including myocardial infarction, stroke and cardiovascular death
- Atherosclerosis
- Chronic Kidney Disease
- Non-alcoholic fatty liver disease (NAFLD)
- Atrial fibrillation
- Heart failure with preserved ejection fraction
- Alzheimer's disease
- Polycystic ovary syndrome (PCOS)

## Patient Group

### Disease Area and Clinical Need

PAD is a common condition in which narrowed arteries reduce blood flow to the arms or legs. PAD is usually caused by a build-up of fatty deposits in the arteries (atherosclerosis). Atherosclerosis causes narrowing of the arteries that can reduce blood flow in the legs and, sometimes, the arms. This may cause leg pain when walking (claudication) and other symptoms. Claudication symptoms include muscle pain or cramping in the legs or arms that begins during exercise and ends with rest. The pain is most commonly felt in the calf and ranges from mild to severe. Severe leg pain may make it hard to walk or do other types of physical activity. PAD treatment includes exercising, eating a healthy diet and not smoking or using tobacco.[7] A number of factors can increase a patients' risk of developing PAD and other forms of cardiovascular disease (CVD), including smoking, diabetes, high blood pressure, high cholesterol and growing older.[8]

Diabetes is a serious condition where blood glucose regulation is impaired and levels can become too high. It can happen when the body doesn't produce enough insulin or the insulin it produces isn't effective. This causes the blood glucose levels to keep rising. Around 90% of people with diabetes in the UK have type 2. It is serious condition and can be lifelong. Having type 2 diabetes without treatment means that high sugar levels in the blood can seriously damage parts of the patients' body, including the eyes, heart and feet.[9] Over time, people who have diabetes and high blood sugar can develop serious or life-threatening complications, including heart disease, stroke, kidney problems, nerve damage, and eye problems. Using medication(s), making lifestyle changes (e.g., diet, exercise, quitting smoking), and regularly checking blood sugar may help to manage diabetes and improve health outcomes.[10]

In 2020-21, in England, there were 52,036 finished consultant episodes (FCE) for T2D (ICD code E11), 29,858 admissions and 180,826 FCE bed days. Furthermore, there were 4,466 finished consultant episodes (FCE) for unspecified peripheral vascular disease (ICD code I73.9), 3,220 admissions and 18,422 FCE bed days.[11]

## Recommended Treatment Options

Treatment options for intermittent claudication include supervised exercise programme, angioplasty and stenting, bypass surgery and graft types and naftidrofuryl oxalate. Treatment options for critical limb ischaemia include revascularisation, painkillers and major amputation.[12]

NICE currently recommends the following treatment options for type 2 diabetes:[13]

- Metformin
- SGLT2 inhibitors
- DPP-4 inhibitors
- Pioglitazone
- Sulfonylureas
- GLP-1 receptor agonists
- Insulin (glargine, detemir, degludec, neutral protamine Hagedorn)

## Clinical Trial Information

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| Trial | **STRIDE,** NCT04560998, EudraCT2019-003399-38; Effects of Semaglutide on Functional Capacity in Patients With Type 2 Diabetes and Peripheral Arterial Disease<br>**Phase III:** Recruiting<br>**Location(s):** US, Canada, 11 EU countries and other countries |

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| | **Primary completion date:** October 2022 |
| Trial Design | Randomised, parallel assignment, quadruple masking |
| Population | N=800 (estimated); adults ages 18 years and older; diagnosed with type 2 diabetes mellitus at least 180 days prior to the day of screening; symptoms of PAD with intermittent claudication in Fontaine stage IIa; screening flat treadmill test (3.2 km/h (2 mph)); Screening constant load treadmill test with fixed inclination of 12% and a fixed speed of 3.2 km/h (2 mph); ankle-brachial-index (ABI) equal to or below 0.90 or toe-brachial index (TBI) equal to or below 0.7. |
| Intervention(s) | Semaglutide is administered subcutaneously once-weekly in addition to standard-of-care treatment for 52 weeks in a dose escalating manner: 0.25 mg from week 1 to week 4, 0.5 mg from week 5 to week 8 and 1.0 mg from week 9 to week 52. |
| Comparator(s) | Placebo given subcutaneously in addition to standard-of-care treatment |
| Outcome(s) | **Primary outcome:**<br>• Change in maximum walking distance on a constant load treadmill test [time frame: from baseline (week 0) to end of treatment (week 52)]<br>See trial record for full list of outcomes |
| Results (efficacy) | - |
| Results (safety) | - |

## Estimated Cost

Semaglutide (Ozempic, Rybelsus) is already marketed in the UK for the treatment of type 2 diabetes mellitus; the 0.25mg/0.19ml, 0.5mg/0.37ml, and 1mg/0.74ml solution for injection costs £73.25. Packs of 30 3mg, 7mg and 14mg tablets cost £78.48.[14]

## Relevant Guidance

### NICE Guidance

- NICE technology appraisal. Rivaroxaban for preventing major cardiovascular events in people with coronary or peripheral artery disease (TA607). October 2019.
- NICE clinical guideline. Peripheral arterial disease: diagnosis and management (CG147). December 2020.
- NICE quality standard guideline. Peripheral arterial disease: diagnosis and management. January 2014.

### NHS England (Policy/Commissioning) Guidance

- NHS England. Action for Diabetes. January 2014.
- NHS England. 2013/14 NHS Standard Contract for Specialised Vascular Services (Adult). A04/S/a

### Other Guidance

- Firnhaber JM and Powell CS. Lower extremity peripheral artery disease: diagnosis and treatment. 2019.[15]
- Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of glycaemic control in people with type 2 diabetes. 2017.[16]
- Scottish Intercollegiate Guidelines Network (SIGN). Management of diabetes. 2017.[17]
- European Society of Cardiology (ESC). Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases. 2017.[18]
- Tran B. Assessment and management of peripheral arterial disease. 2021.[19]

## Additional Information

Novo Nordisk Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

## References

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2 Electronic Medicines Compendium (EMC). *Ozempic 0.25 mg solution for injection in pre-filled pen*. 2021. Available from: https://www.medicines.org.uk/emc/product/9748/smpc#PHARMACOLOGICAL_PROPS.

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