Health Technology Briefing
August 2022

High-dose aflibercept for diabetic macular oedema

Company/Developer	Bayer AG

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 29879	NICE ID: 10621	UKPS ID: 659586

Licensing and Market Availability Plans

Currently in phase II/III clinical trials

Summary

High-dose aflibercept is in clinical development for the treatment of diabetic macular oedema. DMO is swelling of the macula caused by diabetes or by blockage of the veins behind the retina and it is the most common cause of sight loss in people with diabetes. DMO occurs when blood vessels damaged by high blood sugar leak into the central area of the retina (macula), a thin layer of tissue that lines the back of the eye, resulting in a fluid build-up. The risk of developing DMO is greater for people who have had diabetes for a long time, have poorly controlled blood sugar, have high blood pressure, have high cholesterol levels, smoke and are pregnant.

Aflibercept is a type of protein that changes the amount of blood that can get to the retina, in the eye. It works by binding to growth factors that prevents them binding to their receptors. In turn, this prevents activation of the receptors which reduces vascular permeability. High-dose aflibercept, if licenced, would require less frequent injections and monitoring visits. This may improve quality of life for patients and may increase treatment adherence, leading to improved visual outcomes. If licenced, high-dose aflibercept would offer an additional treatment option for patients with visual impairment due to DMO.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.
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Proposed Indication

Treatment of patients with diabetic macular oedema (DMO).

Technology

Description

Aflibercept is an ophthalmological, anti-neovascularisation agent. Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1. Aflibercept acts as a soluble decoy receptor that binds vascular endothelial growth factor-A (VEGFA) and placental growth factor (PlGF) with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors. VEGF-A and PlGF are members of the VEGF family of angiogenic factors that can act[1] as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases; VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF can synergize with VEGF-A in these processes and is also known to promote leucocyte infiltration and vascular inflammation. Aflibercept, therefore, works by changing the amount of blood that gets to the retina.[2,3]

High dose aflibercept is currently in clinical development for diabetic macular oedema. In a phase III clinical trial (NCT04429503), 8mg aflibercept is administered through an injection to the eye every 12 or 16 weeks.[1,4]

Key Innovation

Aflibercept 8mg is a new high-dose formulation for intravitreal injection in adults with visual impairment due to DMO. Currently aflibercept is licensed in the UK at a lower dose of 2mg dose, administered as an injection once every month.[2] A higher dose of aflibercept is not currently licensed. The benefit of higher dosage aflibercept to patients is fewer injections which results in less hospital visits. This will improve quality of life for patients and through, likely improvements to treatment adherence, also improve visual outcomes. This benefit is strongly needed given the already high appointment burden of diabetes and its comorbidities. The associated ease of appointment burden will translate to an increase in NHS capacity.[5,6]

If licenced, high-dose aflibercept will offer an additional treatment option for patients with visual impairment due to DMO.

Regulatory & Development Status

Low-dose aflibercept has Marketing Authorisation in the EU/UK for the following indications:[2]

- Neovascular (wet) age-related macular degeneration
- Visual impairment due to macular oedema secondary to retinal vein occlusion
- Visual impairment due to DMO
- Visual impairment due to myopic choroidal neovascularisation

High dose aflibercept does not currently have Marketing Autorisation in the EU/UK for any indication.

High dose aflibercept is in phase III/II trials for wet age-related macular degeneration.[7]

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Patient Group

Disease Area and Clinical Need

DMO is the most common cause of sight loss in people with diabetes. It affects the central area of the retina, called the macula, which is responsible for fine detail vision both near and far away. DMO occurs when blood vessels damaged by high blood sugar leak into the macular region resulting in a fluid build-up.[8,9] This build-up of fluid causes swelling of the macula which can impair sight. People with type 1 and type 2 diabetes are at risk of DMO. The risk of developing DMO is greater for people who have had diabetes for a long time, have poorly controlled blood sugar, have high blood pressure, have high cholesterol levels, smoke and are pregnant.[10] In the early stages of diabetes a person may not notice any effect on their vision. Damage to the retina occurs over many years. However, when the blood vessels in or close to the macula become damaged, or there is sudden bleeding or fluid leaking into the macula, then sight can worsen dramatically.[8]

According to the UK's national ophthalmology database study in 2013, clinically significant macular oedema was present in 6,664 eyes, 13.9% of the total number of diabetic eyes with structured assessment data at the time of their last record.[11] The prevalence of DMO in the UK diabetic population is approximately 7%.[12] An English 2010 study estimates that ~39% of these patients will have clinically significant DMO reducing the visual acuity to poorer than 6/6 in at least one eye. Approximately 2.7% of UK diabetes patients experience clinically significant DMO with visual impairment.[13] In England (2020/21), there were 581 hospital admissions for patients with type 1 diabetes with ophthalmic complications (ICD-10 code E10.3, which includes DMO), and 839 finished consultant episodes (FCEs), resulting in 1,510 FCE bed days and 293 day cases. There were 962 hospital admissions for patients with type 2 diabetes with ophthalmic complications (ICD-10 code E11.3, which includes DMO), and 1,287 FCEs, resulting in 2,110 FCE bed days and 535 day cases.[14]

Recommended Treatment Options

DMO is usually treated with either laser treatment or intravitreal injections.[15] NICE recommends pharmacological therapies for DMO in eyes with central retinal thickness (CRT) >400 µm. These can either be anti-VEGF injections or steroids. NICE currently recommends the following therapies for the treatment of DMO:[16]

- Ranibizumab
- Aflibercept
- Fluocinolone acetonide
- Dexamethasone

Clinical Trial Information

Trial	**PHOTON**, NCT044239503, 2019-003643-30; A Randomized, Double-Masked, Active-Controlled Phase 2/3 Study of the Efficacy and Safety of High-Dose Aflibercept in Patients With Diabetic Macular Oedema **Phase II/III** – active, not recruiting **Location(s):** 3 EU countries, UK, USA, Canada, Japan and Puerto Rico **Primary Completion Date:** May 2022
Trial Design	Randomised, parallel-assignment, quadruple blinded, active comparator

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Population	N=660; aged 18 years and above; diabetic macular oedema (DMO) with central involvement in the study eye
Intervention(s)	8mg aflibercept injected into the eye every 12 or 16 weeks[4]
Comparator(s)	2mg aflibercept injected into the eye every 8 weeks[4]
Outcome(s)	Primary outcome measure: Change from baseline in best corrected visual acuity See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Aflibercept is already licenced in the UK:[17]

- 3.6mg/90microlitres solution for injection pre-filled syringers costs £816.00.
- 4mg/100microlitres solution for injections costs £816.00.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Ranibizumab port delivery system for treating diabetic macular oedema (GID-TA11065). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Brolucizumab for treating diabetic macular oedema (GID-TA10794). Expected November 2022.
- NICE technology appraisal in development. Faricimab for treating diabetic macular oedema (TA799). June 2022.
- NICE technology appraisal. Aflibercept for treating diabetic macular oedema (TA346). July 2015.
- NICE technology appraisal. Dexamethasone Intravitreal implant for treating diabetic macular oedema (TA349). July 2015.
- NICE technology appraisal. Ranibizumab for treating diabetic macular oedema (TA274). February 2013.
- NICE clinical guideline. Type 2 diabetes in adults: management (NG28). December 2015.
- NICE clinical guideline. Type 1 diabetes in adults: diagnosis and management (NG17). August 2015.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- Amoaku et al. Diabetic retinopathy and diabetic macular oedema pathways and management: UK Consensus Working Group. 2020.[16]
- Scottish Intercollegiate Guidelines Network. Management of diabetes: a national clinical guideline. 2017.[18]
- European Society of Retina Specialists (EURETINA). Guidelines for the management of diabetic macular edema by EURETINA. 2017.[19]
- The Royal College of Ophthalmologists. Diabetic Retinopathy Guidelines. 2012.[20]

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Additional Information

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