National Institute for Health and Care Excellence

Health Technology Evaluation

Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy (review of TA613) [ID6307]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Alimera Sciences Ltd	Yes, Alimera Sciences consider review of [TA613][1] to be necessary and the proposed evaluation route appropriate for three key reasons: 1. Equity of access and addressing an unmet need. 2. Improving patient outcomes. 3. NHS capacity and budgetary constraints **1. Equity of access and addressing an unmet need** The current NICE recommendation for fluocinolone acetonide (FAc) intravitreal implant only allows for reimbursement in the pseudophakic patient population, which does not align with the full marketing authorisation for FAc implant in the UK. The NICE [TA824][2] recommendation lifted the restriction of	Thank you for your comment. NICE will consider the most appropriate evaluation route for this topic. No action needed.

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		access to the dexamethasone intravitreal implant in patients with a natural (phakic) lens. This has thus created an inequity of access in the revised treatment pathway[2] for diabetic macular oedema (DMO) in the UK. Consequently, it perpetuates an unmet need in the natural lens DMO eyes for a longer-acting efficacious therapy that necessitates fewer injections. The FAc implant allows for up to 36-month duration of effect, the dexamethasone implant requires ~2 injections[9],10 a year and anti-VEGF therapies regimens can require an injection frequency of between 14 and 16 injections over a 24-month period.[3] As per [TA824][2] patients preference speak to access to a therapy which can keep "…. the same level of vision with fewer injections".[2] **2. Improving patient outcomes** It has been articulated by the UK clinical and patient communities, and is well-characterised in the literature, that access to a long-acting corticosteroid therapy, in the face of sub-optimal response to anti-VEGF therapies irrespective of lens status, is crucial in optimising patient outcomes. According to Sivaprasad et al ocular injections can be a source of fear, stress, and anxiety for patients with retinal diseases. The frequency of clinic visits, injections, and monitoring required to achieve optimal long-term outcomes results in a high burden of treatment for DMO patients and their caregivers.[4,5] ILUVIEN is a long-acting corticosteroid therapy with a duration of effect for up to 36-months[6,7] and thus helps address patient and caregiver burden through reduced contact visits with the NHS and can thereby improve visual outcomes and health related quality of life when contextualised to patient level experience and voiced preferences.	

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		3. NHS capacity and budgetary constraints Nationally, ophthalmology services represent the second highest throughput for outpatient attendance relative to other medical and surgical conditions. Ophthalmology services recorded the highest level of outpatient activity of all NHS services in 2019-2020 with 7.9 million attendances compared to 7.5 million outpatient appointments in England in 2016/2017.[8] ILUVIEN through its long-acting formulation of up to 36-months[6,7] helps address capacity and resourcing burden issues in an already constrained ocular service within the NHS through its reduced injection frequency when compared to both the dexamethasone intravitreal implant[9,10] and anti-VEGF agents.[3] While ILUVIEN does not represent the panacea to prevailing ocular services issues within the NHS, it does however provide a solution to the post-COVID era where backlogs have been superimposed on an already overwrought service which itself compromises the sustainability of the service into the future. **Proposed Evaluation Route:** The proposed evaluation route i.e., a single technology appraisal using the cost-comparison approach is considered appropriate for the ILUVIEN [TA613][11] review. A cost-comparison vs. dexamethasone intravitreal implant is considered a valid approach as both therapies are corticosteroids and are indicated for use in the DMO pathway following sub-optimal response to anti-VEGF agents.[2] The two therapies offer similar clinical benefits and are only differentiated in	

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		terms of drug release technology. As ILUVIEN has a longer duration of action and lower injection frequency, Alimera Sciences anticipates being able to demonstrate similar benefits for the FAc implant but at a lower cost to the NHS.	
	AbbVie	No comments	Thank you for your comment. No action required.
	Macular Society	The single technology appraisal process using the cost comparison approach is appropriate for this treatment.	Thank you for your comment. No action required.
	Royal College of Ophthalmologists (RCOphth)	The proposed evaluation is appropriate as it will align the use of fluocinolone and dexamethasone implants in the treatment pathway for diabetic macular oedema (DMO). A single technology appraisal is appropriate.	Thank you for your comment. No action required.
Wording	Alimera Sciences Ltd	Alimera Sciences consider the draft remit appropriately reflects the issues of clinical and cost effectiveness for the ILUVIEN technology which warrant consideration by NICE.	Thank you for your comment. No action required.
	AbbVie	No comments	Thank you for your comment. No action required.
	Macular Society	Yes	Thank you for your comment. No action required.

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	Royal College of Ophthalmologists (RCOphth)	Yes. The existing data (registration RCT) on efficacy of fluocinolone in DMO includes eyes that are phakic as well as pseudophakic, and demonstrate clinical similarity in the whole population (similar to dexamethasone). This review will allow for parity with the dexamethasone intravitreal implant, consistent with the approved label for fluocinolone implant (EMA) which covers both the phakic and pseudophakic population.	Thank you for your comment. No action required.
Additional comments on the draft remit	Alimera Sciences Ltd	Alimera Sciences consider the review should be marked as urgent. The All-Party Parliamentary Group on Eye Health and Visual Impairment (June 2018)12 acknowledge how the current system for occular services is failing patients with delays in treatments, and through the cancellation of time-critical appointments. Thus even prior to the pandemic, ophthalmology was the busiest specialty in UK with the highest number of attendances for outpatient appointments, where delays in hospital eye care services were resulting in permanently reduced vision in some patients. Thus, the ophthalmology services in the UK were already struggling with resource pressures prior to the COVID-19 pandemic. Backlogs have only been worsened by the pandemic.13 Access to alternative treatments which have less onerous treatment regimens can reasonably help address current resource and capacity constraints which characterise the NHS ocular services.	Thank you for your comment. This evaluation has been scheduled into the work programme.
	Macular Society	Iluvein is a treatment currently recommended for those with DMO who do not respond to anti-VEGF drugs or for whom they are not an option, if they are pseudophakic. It is not the only steroid drug available for DMO as dexamethasone (Ozurdex) is also approved. However Iluvien is a longer acting drug and may be a more suitable option for some patients as fewer injections will be required. Enabling the use of Iluvien may help to relieve some of the pressure on hospital eye clinics as it is a longer acting treatment	Thank you for your comment. No action required.

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		than dexamethasone. However, patients are still required to attend hospital to have their intraocular pressure monitored every 3 months.	
	Royal College of Ophthalmologists (RCOphth)	Timings are appropriate. It is a useful addition for patients suboptimally responsive to other therapies.	Thank you for your comment. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Alimera Sciences Ltd	Overall, the background information provides a comprehensive summary of the pathophysiology, epidemiology and DMO pathway of care in the NHS. However, in the 2022 NHS commissioning guidelines for DMO[14] reference recently published DMO consensus guidelines[15] which provide an algorithm for clinical assessment of anti-VEGF response and switch to corticosteroid-based therapy in those defined as having a sub-optimal response. The consensus guidelines clearly delineate the sequencing of therapeutic interventions for DMO per the pathway i.e., anti-VEGF therapy, followed corticosteroid therapy. The latter is recommended for DMO patients who have a sub-optimal response to anti-VEGF therapy or for whom anti-VEGF therapy is contraindicated. These guidelines need to be included in the background section as they are critical in enabling a harmonised and structured approach in DMO assessment and therapeutic management. Consider 2 key points:	Thank you for your comment. The scope background has been updated.

Section	Consultee/ Commentator	Comments [sic]	Action
		• Downey et al highlighted that "*30 to 40% of optimally treated DMO patients respond poorly to anti-VEGF with transient or incomplete resolution of fluid*".[15] Some cases of DMO are VEGF-driven and in others, inflammatory mediators play a key role in disease pathology. This can be partly explained by the pro-inflammatory state present since the beginning of the disease that plays a pivotal role in the pathophysiology of early diabetic retinopathy. • Currently available anti-VEGF therapies require frequent injections to achieve outcomes reported in registration studies. The real-world data highlights how anti-VEGF randomised controlled trials (RCT) outcomes are not reflected in the real world due to the challenges in adhering to the onerous RCT treatment regimens.[5,16] Deviation from RCT treatment regimens is mediated by a range of factors which include resource and capacity issues,[16] patient preferences for less frequent injections and associated adherence factors related to regimen burden.[5] The consensus guidelines for patient assessment for the suitability of continued anti-VEGF therapy thus represent an important component of DMO disease management in the NHS.[15,17] The consensus guidelines provide a harmonised algorithm for risk assessment and clinical decision making. The consensus guidance thus provides a step wise approach to patient assessment and recommendation on drug class switch to optimise patient outcomes. The guidance recommends early assessment of effect following commencement of anti-VEGF therapy (after a maximum of 6 months of injection) to identify patients who have sub-optimal response. This allows for early switch to corticosteroid-based therapy.[15] Early switch to corticosteroid therapy following sub-optimal response to anti-VEGF agents improves long-	

Section	Consultee/ Commentator	Comments [sic]	Action
		term visual outcomes and preserves the retina. This has been described in the literature.[15,17]	
	AbbVie	No comments	Thank you for your comment. No action required.
	Macular Society	We would draw your attention to the consensus guidelines for when to consider moving treatment from anti-VEGF to an intravitreal corticosteroid. https://bmjophth.bmj.com/content/bmjophth/6/1/e000696.full.pdf These guidelines are referenced in the NHS 'Updated commissioning recommendations for licensed intravitreal anti-VEGF and corticosteroid treatments in England for medical retinal conditions' published in August 2022. As the most up to date expert view on how to manage DMO in the NHS this advice should be taken into account in the technology appraisal.	Thank you for your comment. The scope background has been updated.
	Royal College of Ophthalmologists (RCOphth)	The most appropriate classification for DMO is whether it is centre-involving or non-centre involving. That is because unlike laser therapy, outcomes for pharmacologic therapies do not depend on the original ETDRS classifications. Treatment is restricted to centre-involving DMO. There is significant suboptimal response to anti-VEGF therapy in DMO (Rennie, C., Lotery, A., Payne, J. et al. Suboptimal outcomes and treatment burden of anti-vascular endothelial growth factor treatment for diabetic macular oedema in phakic patients. Eye (2023). https://doi.org/10.1038/s41433-023-02667-w). This necessitates treatments with steroids that also target non-VEGF pathways.	Thank you for your comment. The scope background has been updated.

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Population	Alimera Sciences Ltd	Yes, the decision problem pertains to a review of ILUVIEN in patients with a natural lens.	Thank you for your comment. No action required.
	AbbVie	No comments	Thank you for your comment. No action required.
	Macular Society	Yes	Thank you for your comment. No action required.
	Royal College of Ophthalmologists (RCOphth)	Yes	Thank you for your comment. No action required.
Subgroups	Alimera Sciences Ltd	No sub-groups were identified as clinically and economically relevant to this assessment.	Thank you for your comment. No action required.
	AbbVie	No comments	Thank you for your comment. No action required.
	Macular Society	No	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Royal College of Ophthalmologists (RCOphth)	Please see under Equality below	Thank you for your comment. No action required.
Comparators	Alimera Sciences Ltd	**The dexamethasone intravitreal implant is considered to be the *only* relevant comparator in this review.** • **Laser photocoagulation alone** is not considered a relevant comparator. • **The following listed anti-VEGF agents alone, or in combination with laser photocoagulation** are not considered relevant comparators. Aflibercept, brolucizumab, ranibizumab, faricimab which are indicated only if the eye has a central retinal thickness of 400 micrometres or more and bevacizumab which does not currently have marketing authorisation in the UK for this indication. The objective of this review is to assess the cost effectiveness of ILUVIEN in DMO patients with a natural lens within the context of the current clinical pathway[2] i.e., following sub-optimal response to anti-VEGF therapy or where anti-VEGF therapy is contraindicated. **The following provides rational as to why laser photocoagulation and anti-VEGF agents are not relevant comparators.** Standard treatment for DMO since the nin-1980s was laser photocoagulation. The introduction of intravitreal anti-VEGF intraocular injections has replaced laser photocoagulation as the mainstay of treatment and is largely first-line therapy for treatment naïve patient presenting with DMO in the NHS. Although they can provide efficacy in most eyes, a sizeable proportion (up to	Thank you for your comment. NICE has decided that this topic is suitable for a cost comparison routing. The scope has been narrowed to only comparators that are appropriate for cost comparison.

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		40%)[15] of eyes do not respond sufficiently. It was acknowledged that many phakic eyes continued to receive anti-VEGF therapy even after it may be optimal.[11] [TA824] has in part addressed the unmet need for phakic eyes. Once sub-optimal response has been identified the current NHS treatment pathway recommends a switch from anti-VEGF agents to corticosteroid therapy. This is supported by the literature whereby timely switch can optimize visual outcomes.[15,18] Anti-VEGF therapy +/- laser therapy occupy an earlier part of the DMO treatment pathway[2] than corticosteroid therapy and therefore are not considered relevant comparators. **The dexamethasone intravitreal implant is the *only* comparator relevant to this assessment.** • Changing treatment to an intravitreal corticosteroid implant at the appropriate time may help optimize patient outcomes irrespective of lens status and reduce injection frequency thereby reducing treatment burden to both the NHS and patient.[15, 16,17,18] • Therapeutic management of DMO within the treatment pathway is thus sequenced, whereby corticosteroids are recommended following sub-optimal response to anti-VEGF therapy or where anti-VEGF therapy is contraindicated. [2] • The cost-effectiveness of the dexamethasone intravitreal implant relative to anti-VEGF therapy in patients with a natural lens was determined by NICE and recommended as per [TA824].[2] In line with updates to the NICE pathways in HTA assessment[19] it is considered that the cost-comparison route is optimal and suitable. Both	

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		ILUVIEN and the dexamethasone intravitreal implant are same class drugs, only differentiated by inherent drug release technology. ILUVIEN has an extended duration of effect for up to 36-months[6,7] and the dexamethasone intravitreal implant has a duration of effect for up to 6-months.[9,10.] On this basis it is considered that the dexamethasone intravitreal implant is the natural comparator for this assessment. The salience of **watch-and-wait as a comparator** must be considered relative to how the treatment pathway has evolved since the [TA824][2] recommendation. As per [TA824] the watch-and-wait population was not considered separately in the supporting economic evidence due to limitations in the evidence base for this population and thus not reported. This limitation and associated uncertainty were accepted by NICE in [TA824]. If a treatment is available with similar efficacy and acceptability, but lower frequency of administration and lower costs in this position in the pathway, it may also be considered in the same a pragmatic fashion to support clinical and patient need.	
	AbbVie	No comments	Thank you for your comment. No action required.
	Macular Society	Since patients with DMO would only be considered for corticosteroid treatment if they were insufficiently responsive to, or not suitable for, anti-VEGF treatment, the only direct comparator would be dexamethasone. The consensus guidelines and NICE guidance leaves the choice of which corticosteroid therapy to use in DMO to the clinical judgement of the ophthalmologist.	Thank you for your comment. NICE has decided that this topic is suitable for a cost comparison routing. The scope has been

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			narrowed to only comparators that are appropriate for cost comparison.
	Royal College of Ophthalmologists (RCOphth)	The comparators are not appropriate for this appraisal, as laser photocoagulation is not used in centre-involving DMO. As such, laser photocoagulation should be excluded. It is to be avoided. Bevacizumab use as a comparator is inappropriate, as it is not standard care in the NHS. Furthermore, it is unlicensed for intravitreal injections in any indication in the UK. See Amoaku, W.M., Ghanchi, F., Bailey, C., Banerjee, S., Banerjee, S., Downey, L., Gale, R., Hamilton, R., Khunti, K., Posner, E. and Quhill, F., 2020. Diabetic retinopathy and diabetic macular oedema pathways and management: UK Consensus Working Group. Eye, 34(1), pp.1-51. DOI: 10.1038/s41433-020-0961-6	Thank you for your comment. NICE has decided that this topic is suitable for a cost comparison routing. The scope has been narrowed to only comparators that are appropriate for cost comparison.
Outcomes	Alimera Sciences Ltd	Outcomes listed are appropriate however we wish to add an outcome measure to the list: **Injection Frequency.** Frequency of injections represents an important outcome measure for inclusion as it presents as a function of two important measures which underpin the cost comparison evaluation of ILUVIEN. They are: • Clinical Capacity Burden: This outcome measure is important when assessing the cost burden on the finite budgetary and capacity resources within the ocular services within the NHS. • Patient and Caregiver Burden. It is well characterised in the literature[4,5.] and through the public consultation response for [TA824][2] that the frequency of injection imposes economic and social impact on	Thank you for your comment. The outcome 'injection frequency' has been added to the scope.

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		patients and caregivers which can negatively influence patients ability to adhere to onerous treatment regimens. Adherence to injection regimens Treatment intensity correlates with visual outcomes.[16] Poorer visual outcomes negatively impact health related quality of life.[20] The [TA824][2] public consultation responses were overwhelming in terms of both need and preference for access to more long-acting therapies in DMO irrespective of lens status. The discernment of the [TA824][2] committee gave due weighting to value-based argumentation on the broader and social dimensions relevant to clinical and patient realities which could not be quantified with necessary precision in EQ-5D and in the empirical data. EQ-5D limitations in ocular conditions are acknowledged and understood.[21,22] Frequency of injection thus represents an important outcome for inclusion in the economic model in [TA613][11] review.	
	AbbVie	No comments	Thank you for your comment. No action required.
	Macular Society	Yes	Thank you for your comment. No change to the scope required.
	Royal College of Ophthalmologists (RCOphth)	Appropriate. The best outcomes are visual acuity and its change with treatment, central retinal thickness in the treated eye, as well as number or frequency of treatment administration. In that regard, the cost-comparison process will	Thank you for your comment. No action required.

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		provide a reliable evidence base to inform this appraisal, as there are to trials comparing the fluocinolone to dexamethasone implant in DMO. It is important to capture the complications of this drug that include raised intraocular pressure and cataract. These rates are much higher than with anti-VEGF agents.	
Equality	Alimera Sciences Ltd	None identified.	Thank you for your comment. No action required.
	AbbVie	No comments	Thank you for your comment. No action required.
	Macular Society	No comment	Thank you for your comment. No change to the scope required.
	Royal College of Ophthalmologists (RCOphth)	Yes. Similar to all TAs for DMO, restricting treatment only for patients with central macular thickness 400 microns is discriminatory as early treatment allows rapid resolution of oedema and for suboptimal responders to anti-VEGF treatment, the switch to steroids can be done early before chronic oedema causes irreversible visual loss.	Thank you for your comment. Where relevant and appropriate, protected characteristics as stated in equality legislation will be considered by the committee during the appraisal. No action required.

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Other considerations	Alimera Sciences Ltd	None identified.	Thank you for your comment. No change to the scope required.
	AbbVie	No comments	Thank you for your comment. No action required.
	Macular Society	None	Thank you for your comment. No change to the scope required.
	Royal College of Ophthalmologists (RCOphth)	None	Thank you for your comment. No change to the scope required.
Questions for consultation	Alimera Sciences Ltd	None identified.	Thank you for your comment. No change to the scope required.
	Macular Society	None	Thank you for your comment. No change to the scope required.
	AbbVie	**Where do you consider fluocinolone acetonide intravitreal implant will fit into the existing care pathway for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy?**	Thank you for your comment. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		No comment **Is laser photocoagulation a relevant comparator for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy?** No **Would fluocinolone acetonide intravitreal implant be a candidate for managed access?** No comment **Do you consider that the use of fluocinolone acetonide intravitreal implant can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** No comment **The full marketing authorisation for fluocinolone acetonide intravitreal implant is "for the treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies".** **Does this mean that fluocinolone acetonide intravitreal implant should only be used after anti-VEGFs and dexamethasone intravitreal implant, or would fluocinolone be given after anti-VEGFs only (at the same point in the treatment pathway as dexamethasone intravitreal implant)?**	

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		No comment **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** **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 fluocinolone acetonide** **intravitreal implant is 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.**	

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		No comment **NICE is considering evaluating this technology through its cost comparison evaluation process.** **Please provide comments on the appropriateness of appraising this topic through this process**. No Comment	
Additional comments on the draft scope	Royal College of Ophthalmologists (RCOphth)	Please see reference Amoaku, W.M., Ghanchi, F., Bailey, C., Banerjee, S., Banerjee, S., Downey, L., Gale, R., Hamilton, R., Khunti, K., Posner, E. and Quhill, F., 2020. Diabetic retinopathy and diabetic macular oedema pathways and management: UK Consensus Working Group. Eye, 34(1), pp.1-51. DOI: 10.1038/s41433-020-0961-6	Thank you for your comment. No change to the scope required.