National Institute for Health and Clinical Excellence

Single/Health Technology Appraisal (STA/MTA)

Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Allergan	We believe that this is an appropriate topic for referral to NICE in order to ensure equitable access to this novel therapy in an area where there are currently no licensed pharmacological agents.	Comment noted. No action required.
	Commissioning Support Appraisals Service (CSAS)	There is no current licensed pharmalogical intervention for this condition	Comment noted. No action required.
	Medicines and Healthcare products Regulatory Agency (MHRA)	Yes, it is a debilitating disease with no current licensed treatments	Comment noted. No action required.
	Royal College of Physicians	Yes, very much so	Comment noted. No action required.
	Royal National Institute of Blind People (RNIB)	We believe that it would be appropriate to refer this topic to NICE for appraisal since there is currently no treatment available for macular oedema caused by central retinal vein occlusion.	Comment noted. No action required.
Wording	Allergan	Yes	Comment noted. No action required.
	CSAS	seems appropriate	Comment noted. No action required.

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	Royal College of Physicians	Yes	Comment noted. No action required.
	RNIB	Yes	Comment noted. No action required.
Timing Issues	Allergan	Retinal vein occlusion represents the second most common form of blindness secondary to retinal vascular disease. As there are no licensed pharmacological agents available for the treatment of this condition which is an important cause of vision loss, this is an area that will benefit greatly from a rapid appraisal and dissemination of guidance to ensure equitable access across England and Wales.	Comment noted. No action required.
	CSAS	It is not clear at which stage of marketing approval submission this drug is at currently although there are two phase III trials which are completed	Comment noted. No action required.
	Royal College of Physicians	Moderate urgency	Comment noted. No action required.
	RNIB	We are not aware of the exact date when the marketing authorisation for the dexamethasone intravitreal implant for CRVO is likely to be granted but believe that it will be important to start the appraisal process to ensure that its outcome is as close to marketing authorisation as possible.	Comment noted. No action required.
Additional comments on the draft remit	Allergan	No	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action

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Background information	Allergan	The background section provides a concise and complete summary. In including commentary around the off-label use of triamcinolone acetonide we note that the manufacturers of this technology have formally recommended against the injection of this product into the vitreous as it was not designed or tested for this purpose.	Consultees indicated that triamcinolone is used outside the licensed indication occasionally in the NHS and therefore remains in the scope as a comparator.
	CSAS	The background information appears accurate	Comment noted. No action required.
	Royal College of Physicians	Reasonable for accuracy and completeness	Comment noted. No action required.
	RNIB	The background information refers to treatments that are currently not available in this country (triamcinolone) or have been shown to be ineffective (laser photocoagulation). This should be mentioned in this section.	Consultees indicated that triamcinolone is used outside the licensed indication occasionally in the NHS and therefore remains in the scope as a comparator.
The technology/ intervention	Allergan	In describing the technology, we suggest inclusion of a statement regarding duration of action. For example: "It is a biodegradable implant with is delivered by intravitreal injection (IVT) where it delivers dexamethasone to the posterior segment of the eye for up to six months."	Inserted ‘for up to 6 months’ as suggested.
	CSAS	The description of the technology is accurate however the scope should also mention the length of time the implant functions in the eye, as this will have economic and patient satisfaction implications over multiple injections of comparator treatments	This detail will be considered during an appraisal and is not appropriate for inclusion in the scope.
	Royal College of Physicians	Yes	Comment noted. No action required.
	RNIB	Yes	Comment noted. No action required.

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Population – *is the population defined appropriately? Are there groups within this population that should be considered separately?*	Allergan	Yes. With regards to separate populations, the term Retinal vein occlusion encompasses both Central Retinal Vein Occlusion (CRVO) and Branch Retinal Vein Occlusion (BRVO), which have been captured within the clinical studies outlined	Comment noted. No action required.
	CSAS	The population appears to be defined appropriately	Comment noted. No action required.
	MHRA	Duration of macular oedema at baseline	This has been included as a subgroup in the scope.
	Royal College of Physicians	Yes	Comment noted. No action required.
	RNIB	The population is defined appropriately and there are no groups within this population that should be considered separately.	Comment noted. No action required.
Comparators	Allergan	Arguably none of the comparators listed are valid as these are unlicensed, unproven treatments that have been used in the absence of a licensed therapeutic option. As per the previous comment on triamcinolone acetonide, the manufacturer of this has formally recommended against its ocular use. Standard care for CRVO in the UK should be considered to be observation based on the results of previous randomised controlled studies. In the case of BRVO, some patients are suitable for treatment with laser photocoagulation. Patients with foveal ischemia, or intra-retinal haemorrhage may not be considered appropriate patients for laser treatment; in this patient population observation could once again be considered standard care.	Consultees indicated that bevacizumab and triamcinolone are used outside the licensed indication occasionally in the NHS and therefore they remain in the scope as comparators.

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	CSAS	None of the listed comparators are licensed for this indication therefore published comparative data may be limited. In the clinical trials a sham injection was used as a placebo comparator. A placebo comparator should be added. Arteriovenous crossing sheathotomy is only used for BRVO with special arrangements for consent and for audit or research according to NICE guidance published in 2004 as the safety and efficacy evidence not being adequate. Photocoagulation and photodynamic therapies are used but there are differences in their use between CRVO and BRVO	Consultees indicated that bevacizumab and triamcinolone are used outside the licensed indication occasionally in the NHS and therefore they remain in the scope as comparators. Consultees suggested that surgical techniques are not used in clinical practice and have not been included in the scope. Consultees considered that photocoagulation would not necessarily be used to treat CRVO, but to treat neovascularisation and therefore considered that photocoagulation would be a comparator for non-ischaemic BRVO only.
	Royal College of Physicians	There is no known treatment to improve vision in CRVO. We believe it would be reasonable to have no treatment as a comparator.	Consultees suggested that Best Supportive Care is often the only treatment option and the scope will be amended to include this as a comparator for CRVO and ischaemic BRVO.

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	RNIB	There are no standard treatments used in the NHS that are licensed for this indication. Triamcinolone is not available for intraocular administration and bevacizumab is only licensed for use in oncology. We believe that it would be inappropriate to compare ranibizumab for use in CRVO with bevacizumab since no large-scale trials have taken place to determine the safety and efficacy of bevacizumab and it is unlikely that the manufacturer of bevacizumab will apply for a licence for bevacizumab to be used in this indication. The only appropriate comparator is therefore best supportive care (rather than best alternative care).	Consultees indicated that bevacizumab and triamcinolone are used outside the licensed indication occasionally in the NHS and therefore they remain in the scope as comparators. Consultees suggested that Best Supportive Care is often the only treatment option and the scope will be amended to include this as a comparator for CRVO and ischaemic BRVO.
Outcomes	Allergan	As RVO is predominantly a monocular disease at first presentation, BCVA in the affected eye is the most important measure of health related benefit. This can be considered in several different ways: patients gaining lines (or letters) of vision, patients losing lines (or letters) of vision and the time in which these benefits are achieved are all potentially important measures. Contrast sensitivity is rarely measured in UK clinical practice and so is unlikely to add value in the context of the review. From an anatomical perspective, retinal thickness (assessed by OCT) can also be a useful prognostic indicator of response to treatment and resolution of oedema.	No change to outcomes in scope – consultees considered that the current list of outcomes covered the most important outcomes.
	CSAS	The outcomes appear appropriate	Comment noted. No action required.
	MHRA	An additional important outcome measure would be time to achieve improvement in visual acuity	No change to outcomes in scope – consultees considered that the current list of outcomes covered the most important outcomes.

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	Royal College of Physicians	Yes	Comment noted. No action required.
	RNIB	We are slightly puzzled by the expression (visual acuity - the whole person). Does this mean visual acuity in both eyes or visual acuity in the better seeing eye as opposed to visual acuity in the worse seeing eye? It is not an expression that is generally used when referring to visual acuity. If it is intended to mean that visual field measurements are included this should be specified.	The outcome visual acuity – the whole person takes into account a person's full visual ability whereas visual acuity – the affected eye is an outcome which specifically measures change in the affected eye only.
Economic analysis	Allergan	We believe that a life-time horizon is of greatest relevance in this population.	Comment noted. No action required.
	Royal College of Physicians	No comment	Comment noted. No action required.
	RNIB	We appreciate that NICE appraisals focus on costs to the NHS and Personal Social Services. However, particularly where people with a visual impairment in one eye develop CRVO in the second eye the resulting binocular vision impairment has major cost implications in terms of informal care and also loss of productivity (depending on the patient's age). We feel that these costs should be highlighted as part of NICE's assessment of the burden of disease caused by a condition.	The outcome visual acuity – the whole person takes into account a person's full visual ability whereas visual acuity – the affected eye is an outcome which specifically measures change in the affected eye only.

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Equality and Diversity	Allergan	A timely NICE STA will help to ensure appropriate and equitable access across England and Wales; avoiding the so-called "NICE blight" whereby PCTs may feel reluctant to fund therapy in the absence of National guidance. Whilst any STA process is underway, it would be appropriate to reinforce the position taken by the Department of Health, whereby the absence of guidance from NICE is not a reason to not provide funding for a new therapy. In a disease that presents initially monocularly, it is important to consider the impact that monocular vision loss has on HRQoL but also to consider the possibilities of a vision-reducing condition or incident affecting the fellow eye. Studies have sought to explore the rate of occurrence of RVO in fellow eye amongst patients initially affected monocularly and this is up to 3% per year.	Comment noted. No action required. The outcome visual acuity – the whole person takes into account a person's full visual ability whereas visual acuity – the affected eye is an outcome which specifically measures change in the affected eye only.
	CSAS	There are no factors identified which would compromise equality	Comment noted. No action required.
	Royal College of Physicians	As the incidence of CRVO inceases with age it may be worth asking Age Concern for a contribution. We are not aware of any difference in incidence of CRVO between racial groups	Consultees at the scoping workshop recognised that, whilst prevalence of macular oedema is higher in people over the age of 50, this was not classed an equalities issue as it does not affect equity of access to treatment. Therefore no changes to the draft scope are necessary.
Other considerations	Allergan	Where the techology will be administered and the resources required. It is our expectation that existing infrastructure, put in place to support intra-vitreal injections in wet age-related AMD will be adequate for this purpose.	Comment noted. No action required.
	MHRA	consideration may also be given to the duration of macular oedema at baseline.	Comment noted. No action required.

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	Royal College of Physicians	Ischaemic branch retinal vein occlusion could be considered as well	Ischaemic BRVO will be included in the scope.
	RNIB	See above comments on including the costs of informal care and loss of productivity into the appraisal.	See above response.
Questions for consultation	Allergan	Laser photocoagulation is a valid comparator in some sub-groups of patients with Macular Oedema following BRVO. It is not an effective or recommended treatment for macular oedema following CRVO. Additionally, there are some important sub-groups of patients with macular oedema following BRVO who are not suitable candidates for laser therapy. These include patients with foveal ischemia, patients with an intra-retinal haemmorhage with central involvement, and patients with a macular oedema of less than 90 days at presentation. The other comparators listed have been used in clinical practice as no licensed treatments have been available for this condition. However they are not licensed and are not supported by robust, phase 3 data to inform assumptions surrounding efficacy, safety and appropriate dosing.	Consultees considered that photocoagulation would not necessarily be used to treat CRVO, but to treat neovascularisation and therefore considered that photocoagulation would be a comparator for non-ischaemic BRVO only.
Additional comments on the draft scope.	Allergan	No	Comment noted. No action required.

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Value of innovation – relevant benefits and outcomes	Allergan	In terms of relevant clinical outcomes and health related benefits associated with OZURDEX in the treatment of macular oedema following RVO; our clinical study programme allows an assessment of both functional (benefits on improving visual acuity) and anatomical measures (reductions in oedema as determined by OCT), and additionally an assessment of patient reported outcomes to inform an understanding of HRQoL. There are no pharmacological comparator data available as there are no licensed pharmacotherapies available to treatment this condition. The potential for indirect comparison is limited by important differences between trial populations and protocols, particularly around the duration of macular oedema present at baseline, allowing rescue laser photocoagulation during the study and the visual acuity or OCT criteria for re-treatment with a pharmacological agent	Comment noted. No action required.
	CSAS	This will be one of the first pharmacological agents licensed for the treatment of macular oedema secondary to BRVO and CRVO	Comment noted. No action required.
Value of innovation – nature of data	Allergan	Pooled data is available from 2 large, multicentre controlled trials which present efficacy data compared with sham up until six months, followed by a 6 month open label extension. Some of this data has been presented in abstract form and a full publication is currently under peer review.	Comment noted. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

National Public Health Service for Wales (now part of Public Health Wales NHS Trust)
Royal College of Nursing
Department of Health
Welsh Assembly Government
RICE - Research Institute for the Care of Older People