NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA298; Ranibizumab for treating choroidal neovascularisation associated with pathological myopia

This guidance was issued in November 2013.

The review date for this guidance is March 2016.

1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remit(s)

To appraise the clinical and cost effectiveness of ranibizumab within its licensed indication for the treatment of choroidal neovascularisation associated with pathological myopia.

3. Current guidance

1.1. Ranibizumab is recommended as an option for treating visual impairment due to choroidal neovascularisation secondary to pathological myopia when the manufacturer provides ranibizumab with the discount agreed in the patient access scheme

4. Rationale[1]

Limited new evidence has been published since Technology Appraisal 298, and no evidence has been identified that suggests a review of this guidance is necessary.

5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal.

6. New evidence

The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from March 2012 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

the ‘Summary of evidence and implications for review’ section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

The updated literature search found that limited new evidence has been published since Technology Appraisal 298 (TA298) was published. The search identified 5 newly published clinical trials, 2 ongoing trials and 4 systematic reviews, as well as 5 new publications from the RADIANCE and REPAIR studies (which were included in the evidence considered in TA298).

Two small clinical trials (Cha et al. 2014; Pece et al. 2014; 64 and 78 eyes respectively) and 3 systematic reviews (Loutfi et al. 2015; Stuart et al. 2015; Wong et al. 2015) report comparisons of ranibizumab with bevacizumab; in TA298, the Committee highlighted the limited evidence for this comparison as an uncertainty. The results of these studies suggest that ranibizumab and bevacizumab are similar in efficacy, although Loutfi et al. found a statistically significant difference in favour of ranibizumab in 1 outcome. These findings are consistent with the Committee’s conclusions, but the evidence for the comparison of ranibizumab with bevacizumab remains limited.

In TA298, the Committee noted that there was uncertainty about the longer-term clinical effectiveness of ranibizumab (that is, after more than 3 months). Four clinical trials (Carvalho et al. 2014; Cha et al. 2014; Ladaique et al. 2015; Ruiz-Moreno et al. 2015) and 2 systematic reviews (Wang and Chen 2014; Zhou et al. 2014) provide clinical effectiveness evidence after 12 months or more. These studies consistently suggest that the effectiveness of ranibizumab is maintained. This reduces the uncertainty in the evidence and does not suggest that a review of the guidance is needed. Notably, Ruiz-Moreno et al. presented a retrospective case-series study with up to 6 years of follow-up. The authors reported that the efficacy of ranibizumab is maintained for 3 years, although not beyond this point. This finding is not consistent with the company’s economic model in TA298, in which they assumed that efficacy would be maintained indefinitely. However, the Committee noted that ranibizumab remained cost effective even when the duration of effect was reduced, so incorporating this evidence into the model would be unlikely to affect the guidance.

Ladaique et al. (2015) presents evidence on the number of ranibizumab injections that people have in the second year of treatment in clinical practice. This variable was uncertain at the time of TA298. The study suggests that people may have fewer injections than assumed by the company in its model, supporting the cost effectiveness of ranibizumab. In addition, 2 of the ongoing studies (OLIMPIC and BRILLIANCE) are likely to provide further evidence on treatment frequency and re-treatment strategies. Given that ranibizumab remained cost effective even when the number of ranibizumab injections increased, it is not expected that these studies would affect the recommendations in TA298 and so deferring the review of the guidance until these studies report would be of limited value.

Since TA298 was published, 1 new technology – aflibercept, has received a marketing authorisation for treating choroidal neovascularisation associated with pathological myopia. Aflibercept is currently being considered for a technology

appraisal. If an appraisal proceeds, any relevant comparisons between aflibercept and ranibizumab will be captured in that appraisal. It is therefore not necessary to review TA298, as aflibercept would not be established NHS practice, and therefore not a comparator, in any review of TA298. No other clinical or economic factors that would affect the need to review TA298 have been identified.

8. Adoption and Impact

No submission was received from the Adoption and Impact team.

9. Equality issues

No equality issues were raised in Technology Appraisal 298.

GE paper sign off: Frances Sutcliffe, 20 June 2016

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the [specify STA or MTA] process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

- Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion (2013) NICE technology appraisal guidance 283.
- Ranibizumab for the treatment of diabetic macular oedema (rapid review of TA237) (2013) NICE technology appraisal guidance 274.
- Ranibizumab and pegaptanib for the treatment of age related macular degeneration (2008) NICE technology appraisal guidance 155.

Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
"The treatment of visual impairment due to choroidal neovascularisation secondary to pathologic myopia." "The list price of ranibizumab 10 mg/ml is £742.17 per 0.23‑ml vial (excluding VAT; 'British national formulary' [BNF] edition 66)".	The indication is the same, as is the list price – the current (January 2016) BNF gives the NHS indicative price as "£742.00 (Hospital only)".

Details of new products

Drug (company)	Details (phase of development, expected launch date)	In topic selection
Aflibercept (Bayer) for visual impairment due to myopic choroidal neovascularisation (myopic CNV).	Launched in the UK January 2016.	In Topic Selection (TS 8101) and listed in the Topic selection technology appraisal decisions: January - December 2015

Ranibizumab (Novartis) for "Choroidal neovascularization (CNV) and macular oedema (ME) secondary to conditions other than macular degeneration, diabetic macular oedema retinal vein occlusion and pathologic myopia"	The Novartis website appears to indicate filing in 2016.	In Topic Selection (TS 7705) and listed in the Topic selection technology appraisal decisions: January - December 2015

Registered and unpublished trials

Trial name and registration number	Details
NCT02034006 A 12-month, Open-label, Interventional, Multicentre Study to Investigate the Current Criteria Driving Re-treatment With Ranibizumab Upon Relapse in Patients With Visual Impairment Due to Choroidal Neovascularization Secondary to Pathologic Myopia OLIMPIC CRFB002FIT01	Phase III, non-randomised trial. Status: ongoing not recruiting. Primary completion date: July 2016. Enrolment: 200. Primary outcome measures: Describe current criteria driving re-treatment in patients experiencing a relapse after first ranibizumab injection [Time Frame: Baseline to month 12].
NCT01922102 A 12-month, Phase III, Randomized, Double-masked, Multicenter, Active-controlled Study to Evaluate the Efficacy and Safety of Two Individualized Regimens of 0.5mg Ranibizumab vs. Verteporfin PDT in Patients With Visual Impairment Due to Choroidal Neovascularization Secondary to Pathologic Myopia. BRILLIANCE CRFB002F2302	Phase III, randomised trial. Status: currently recruiting. Primary completion date: October 2016. Enrolment: 475. Primary outcome measures: change from baseline BCVA to the average level of BCVA (letters) over all monthly post-baseline assessments: BCVA change; by measuring BCVA score at 4 meters distance using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts [Time Frame: Month 1 to Month 3]

Trial name and registration number	Details
NCT01840410 A 12-month, Randomized, Double-masked, Sham-controlled, Multicenter Study to Evaluate the Efficacy and Safety of 0.5mg Ranibizumab Intravitreal Injections in Patients With Visual Impairment Due to VEGF-driven Choroidal Neovascularization. CRFB002G2301; 2012-005417-38	Phase III, randomised trial. Status: ongoing not recruiting. Primary completion date: December 2015. Enrolment: 183. Primary outcome measures: Best-corrected visual acuity (BCVA) change from baseline to Month 2 in study eye [Time Frame: Baseline and Month 2]

References

Carvalho B, Freitas-Costa P, Pinheiro-Costa J et al. (2014) Evaluation of antiangiogenic treatment results in choroidal neovascularization related to pathological myopia. *Acta Medica Portuguesa.* 27 (1): 49-58.

Cha DM, Kim TW, Heo JW et al. (2014) Comparison of 1-year therapeutic effect of ranibizumab and bevacizumab for myopic choroidal neovascularization: a retrospective, multicenter, comparative study. *BMC ophthalmology.* 14 (69).

Ladaique M, Dirani A, Ambresin A (2015) Long-term follow-up of choroidal neovascularization in pathological myopia treated with intravitreal ranibizumab. *Klinische Monatsblatter fur Augenheilkunde.* 232 (4): 542-547.

Loutfi M, Siddiqui MR, Dhedhi A et al. (2015) A systematic review and meta-analysis comparing intravitreal ranibizumab with bevacizumab for the treatment of myopic choroidal neovascularisation. *Saudi Journal of Ophthalmology.* 29 (2): 147-155.

Pece A, Milani P, Monteleone C et al. (2014) A randomized trial of intravitreal bevacizumab vs. ranibizumab for myopic CNV. *Graefe's Archive for Clinical and Experimental Ophthalmology.* 253 (11): 1867-1872.

Ruiz-Moreno JM, Montero JA, Araiz J et al. (2015) Intravitreal anti-vascular endothelial growth factor therapy for choroidal neovascularization secondary to pathologic myopia: Six years outcome. *Retina.* 35 (12): 2450-2456.

Stuart A, Ford JA, Duckworth S et al. (2015) Anti-VEGF therapies in the treatment of choroidal neovascularisation secondary to non-age-related macular degeneration: a systematic review. *BMJ Open.* 5 (4): e007746-.

Wang E, Chen Y (2014) Intravitreal anti-vascular endothelial growth factor for choroidal neovascularization secondary to pathologic myopia: Systematic review and meta-analysis. *Retina.* 33 (7): 1375-1392.

Wong TY, Ohno-Matsui K, Leveziel N et al. (2015) Myopic choroidal neovascularisation: Current concepts and update on clinical management. *British Journal of Ophthalmology.* 99 (3): 289-296.

Zhou L, Xing YQ, Li T et al. (2014) Meta-analysis of best corrected visual acuity after treatment for myopic choroidal neovascularisation. *Database of Abstracts of Reviews of Effects.* (2): 720-725.