NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA346; Aflibercept for treating diabetic macular oedema and TA349; Dexamethasone intravitreal implant for treating diabetic macular oedema

Original publication date:	22 July 2015
Review date	July 2018
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA346 and TA349 see Appendix A.

1. Proposal

We propose that TA346 and TA349 should be transferred to the 'static guidance list'.

Rationale

There is no new clinical or cost-effectiveness evidence that would warrant reconsideration of the existing recommendations.

For TA346, longer term results of the VISTA and VIVID trials are now available and show similar results to the network meta-analysis results presented in the original guidance. They did not show different trends in terms of effectiveness in the subgroup analyses (i.e. people with a CRT of less or more than 400 micrometres).[1-4]

For TA349, longer term results of the MEAD and BEVORDEX trials are now available as well as additional studies. The results from these are in line with the clinical evidence base that was considered during the development of the guidance and are unlikely to change the optimised recommendation to the full population.[5-14]

2. Summary of new evidence and implications for review

Has there been any change to the price of the technologies since the guidance was published?
TA346 (aflibercept) the list price and PAS has not changed since TA346. TA349 (dexamethasone) the list price has not changed since TA349.
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
No proposed changes to the marketing authorisations.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

No research recommendations were outlined in the original guidance.

For TA346, the main area of uncertainty was that evidence on the comparative effectiveness was only available from a post-hoc analysis of pooled data from two trials (VIVID and VISTA). The ERG conducted this analyses and commented on its limitations (the analysis broke randomisation and was based on small patient numbers). Longer term data are now available from these trials, but would not address the limitations of this analyses. The results are also similar to the earlier data cuts used during TA346.

For TA349, there were 3 important uncertainties:

- The population of the main trial (MEAD trial) was broader than the marketing authorisation. Therefore the company provided subgroup analysis results.
- The comparator arm of the trial (sham procedure/watch-and-wait) did not reflect general diabetic macular oedema patients. It was considered likely that the trial underestimated the benefit of dexamethasone in the overall population compared with watch-and-wait.
- A direct comparison with the other comparators was not available in the subpopulations, therefore a network meta-analysis was conducted. More specifically for the comparison with:
    - ranibizumab in people with a pseudophakic lens with a CRT of 400 micrometres or more,
    - laser photocoagulation or bevacizumab in people with a pseudophakic lens with a CRT less than 400 micrometres,
    - fluocinolone acetonide intravitreal implant in people with a pseudophakic lens and whose chronic DMO does not respond to non‑corticosteroid treatment,
    - watch‑and‑wait for people who do not have a pseudophakic lens and whose DMO does not respond to non‑corticosteroid treatment, or for whom such treatment is unsuitable.

Longer term data from MEAD and BEVORDEX, the trials used in TA349, are now available. New evidence is also available from further studies. However the conclusions of these studies are comparable with those in TA349. In addition, these new data would not enable comparisons of the specific subgroups, as required in the appraisal.

Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

See Appendix C for a list of related NICE guidance.

Additional comments
NA

The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from January 2014 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 the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

3. Equality issues

No issues relating to equality considerations were raised in the submissions, or in the Committee meetings for either of the guidance.

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Appendix A – Information from existing guidance

4. Original remit

TA346: To appraise the clinical and cost effectiveness of aflibercept within its licensed indication for treating diabetic macular oedema.
TA349: To appraise the clinical and cost effectiveness of dexamethasone intravitreal implant within its licensed indication for treating diabetic macular oedema.

5. Current guidance

TA346

1.1 Aflibercept solution for injection is recommended as an option for treating visual impairment caused by diabetic macular oedema only if:

- the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and
- the company provides aflibercept with the discount agreed in the patient access scheme.

1.2 People whose treatment with aflibercept is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue aflibercept until they and their NHS clinician consider it appropriate to stop.

TA349

1.1 Dexamethasone intravitreal implant is recommended as an option for treating diabetic macular oedema only if:

- the implant is to be used in an eye with an intraocular (pseudophakic) lens and
- the diabetic macular oedema does not respond to non‑corticosteroid treatment, or such treatment is unsuitable.

1.2 People whose treatment with dexamethasone intravitreal implant was started within the NHS before this guidance was published, but is not recommended for them by NICE in this guidance, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

6. Research recommendations from original guidance

TA346: N/A
TA349: N/A

7. Cost information from original guidance

TA346: The list price of aflibercept is £816.00 per vial (excluding VAT; British national formulary [BNF] edition January 2015). The total cost for treating a patient in the first year is £6936 (based on 8.5 aflibercept injections). The company has agreed a patient access scheme with the Department of Health. This scheme provides a

simple discount to the list price of aflibercept, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence.

TA349: The list price of dexamethasone intravitreal implant is £870.00 per 700 micrograms (excluding VAT; British national formulary, accessed online January 2015). In the company's model, dexamethasone intravitreal implant was assumed to have a total cost of £986.68 for treating unilateral disease and £1944.19 for bilateral disease.

Appendix B – 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 Technology Appraisal 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 a specific trail.	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

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	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
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

1. Relevant Institute work

Published

NICE technology appraisal guidance 301 (November 2013) Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy. Reviewed: November 2016. Recommendation was a part-review and part re-issue of the guidance.

NICE technology appraisal guidance 274 (February 2013) Ranibizumab for treating diabetic macular oedema Reviewed: April 2015. Decision – transfer to static guidance list.

NICE Medtech innovation briefing 144 (April 2018) Noctura 400 Sleep Mask for diabetic retinopathy and diabetic macular oedema

Suspended/terminated

NICE technology appraisal guidance. Macular oedema (diabetic) - pegaptanib sodium [ID452]. Suspended July 2011 as the manufacturer withdrew their licensing application

NICE technology appraisal guidance. Diabetic retinopathy - ruboxistaurin [ID382]. Suspended April 2007 as the manufacturer withdrew regulatory applications in relation to ruboxistaurin

2. Details of new products

Drug (company)	Details (phase of development, expected launch date)	In topic selection
[redacted]	[redacted]	[redacted]

3. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
Dexamethasone intravitreal implant has a marketing authorisation in the UK for 'the treatment of adult patients with visual impairment due to diabetic macular oedema who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for, non‑corticosteroid therapy'.	No planned change to indication. Dexamethasone 700 microgram: £870 (no change)
Aflibercept has a UK marketing authorisation for 'the treatment of adults with visual impairment due to diabetic macular oedema'.	No planned change to indication Aflibercept 2mg/50microlitres solution for injection vials: £816 (no change)

4. Registered and unpublished trials

Trial name and registration number	Details
Trials involving aflibercept	
Predictors of Treatment Response to Aflibercept and Aqueous Cytokine Levels in Patients With Persistent Diabetic Macular Edema Following Treatment With Ranibizumab: An Interventional Prospective Study (NCT02651168)	Enrolment: 50 participants Start Date: March 2016 Study Completion Date: June 2018 Not yet recruiting

Appendix C

Trial name and registration number	Details
Effect of Aflibercept (Eylea®) in the Management of Bevacizumab (Avastin®) Resistant Diabetic Macular Edema (NCT02924987)	Enrolment: 50 participants Study Start Date: November 2016 Study Completion Date: November 2017 Recruiting
Long-Term Efficacy and Safety of Intravitreal Aflibercept Injections for the Treatment of Diabetic Macular Edema in Subjects Who Completed the Three Year VISTA-DME Trial (The Endurance 2 Trial) (NCT02368756)	Enrolment: 16 participants Study Start Date: December 2014 Study Completion Date: December 2017 Completed
Long-Term Efficacy and Safety of Aflibercept Intravitreal Injections for the Treatment of Diabetic Macular Edema in Subjects Who Completed the Three Year VISTA-DME Trial (NCT02734407)	9 participants Study Start Date: January 2015 Study Completion Date: April 2018 Enrolling by invitation
Randomized Trial of Intravitreous Aflibercept Versus Intravitreous Bevacizumab + Deferred Aflibercept for Treatment of Central-Involved Diabetic Macular Edema (NCT03321513)	260 participants Study Start Date: December 2017 Study Completion Date: December 2019 Recruiting
Long-Term Efficacy and Safety of Intravitreal Aflibercept Injections for the Treatment of Diabetic Macular Edema in Subjects Who Completed the Three Year VISTA-DME Trial (NCT02299336)	26 participants Study Start Date: October 2014 Study Completion Date: February 2017 Completed
An Open-label, Randomized, Active-controlled, Parallel-group, Phase-3b Study of the Efficacy, Safety, and Tolerability of Three Different Treatment Regimens of 2 mg Aflibercept Administered by Intravitreal Injections to Subjects With Diabetic Macular Edema (DME) (NCT02818998)	463 participants Study Start Date: November 16, 2016 Study Completion Date: November 5, 2019 Active, not recruiting

Trial name and registration number	Details
Treatment for Central-Involved Diabetic Macular Edema in Eyes With Very Good Visual Acuity (NCT01909791)	702 participants Study Start Date: October 2013 Estimated Study Completion Date: August 2018 Recruiting
Treat and Extend Versus Dosing Every Eight Weeks With Intravitreal Aflibercept Injections for the Treatment of Diabetic Macular Edema (EVADE Study) (NCT02392364)	50 participants Study Start Date: April 15, 2015 Study Completion Date: November 2018 Active, not recruiting
Single Arm, Single Dose Clinical Study to Investigate Efficacy of Treat-and-Extend Regimen of Intravitreal Aflibercept Injection in Diabetic Macular Edema (NCT02788877)	48 participants Study Start Date: April 2016 Study Completion Date: September 2019 Recruiting
Intravitreous Anti-Vascular Endothelial Growth Factor Treatment for Prevention of Vision Threatening Diabetic Retinopathy in Eyes at High Risk (NCT02634333)	322 participants Study Start Date: January 2016 Study Completion Date: January 2022 Recruiting
Trials involving dexamethasone	
Dexamethasone Intravitreal Implant (0.7mg) for the Treatment of Persistent Diabetic Macular Edema Following Intravitreal Anti-Vascular Endothelial Growth Factor Therapy (NCT024716)	40 participants Study Start Date: June 2015 Study Completion Date: September 2018 Active, not recruiting

5. Implementation

No report.

Appendix D – References

1. Dhoot DS, Baker K, Saroj N, et al. (2018) Baseline Factors Affecting Changes in Diabetic Retinopathy Severity Scale Score After Intravitreal Aflibercept or Laser for Diabetic Macular Edema: Post Hoc Analyses from VISTA and VIVID *Ophthalmology* 125 (1): 51-56.
2. Do D (2016) Intravitreal aflibercept injection (IAI) for diabetic macular edema (DME): 148-week results from VISTA and VIVID Investigative ophthalmology and visual science. Conference: 2016 annual meeting of the association for research in vision and ophthalmology, ARVO 2016. United States 57 (12): 2081.
3. Mitchell P, McAllister I, Larsen M, et al. (2018) Evaluating the Impact of Intravitreal Aflibercept on Diabetic Retinopathy Progression in the VIVID-DME and VISTA-DME Studies Ophthalmology Retina.
4. Wykoff C, Marcus D, Midena E, et al. (2017) Intravitreal aflibercept injection in eyes with substantial vision loss after laser photocoagulation for diabetic macular edema subanalysis of the vista and vivid randomized clinical trials JAMA ophthalmology 135 (2): 107-114.
5. Aroney C, Fraser-Bell S, Lamoureux EL, et al. (2016) Vision-Related Quality of Life Outcomes in the BEVORDEX Study: A Clinical Trial Comparing Ozurdex Sustained Release Dexamethasone Intravitreal Implant and Bevacizumab Treatment for Diabetic Macular Edema Investigative ophthalmology & visual science 57 (13): 5541-5546.
6. Callanan D, Loewenstein A, Patel S, et al. (2016) A multicenter, 12-month randomized study comparing dexamethasone intravitreal implant with ranibizumab in patients with diabetic macular edema Graefe's archive for clinical and experimental ophthalmology: 1-11.
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9. Fraser-Bell S, Lim L, Campain A, et al. (2014) Randomised clinical trial of intravitreal bevacizumab versus intravitreal dexamethasone for diabetic macular oedema. The bevordex study Clinical and experimental ophthalmology. 42: 26-27.
10. Fraser-Bell S, Lim L, Campain A, et al. (2015) A randomized clinical trial of intravitreal bevacizumab versus intravitreal dexametha-sone for diabetic macular oedema: The bevordex study. 2year results Clinical and Experimental Ophthalmology 43 (Supplement 1): 25.
11. Fraser-Bell S, Lim LL, Campain A, et al. (2016) Bevacizumab or Dexamethasone Implants for DME: 2-year Results (The BEVORDEX Study) Ophthalmology 123 (6): 1399-401.
12. Gillies MC, Lim LL, Campain A, et al. (2014) A randomized clinical trial of

intravitreal bevacizumab versus intravitreal dexamethasone for diabetic macular edema: the BEVORDEX study Ophthalmology 121 (12): 2473-81.
13. Gillies MC, Lim LL, Campain AE, et al. (2015) BEVORDEX-A multicentre randomized clinical trial of intravitreal dexamethasone versus intravitreal bevacizumab for persistent diabetic macular edema Investigative Ophthalmology and Visual Science 56 (7): 3144
14. Lim LL, Qatarneh D, Hodgson L, et al. (2016) Progression of diabetic retinopathy in the Bevordex study: A randomized clinical trial of intravitreal bevacizumab versus intravitreal dexamethasone for diabetic macular edema Investigative Ophthalmology and Visual Science 57 (12): 2106.