Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237).

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237). London (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Apr. 75 p. (Technology appraisal guidance; no. 274).

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

This guidance replaces National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance 237 (published in November 2011).

Ranibizumab is recommended as an option for treating visual impairment due to diabetic macular oedema only if:

- The eye has a central retinal thickness of 400 micrometres or more at the start of treatment and
- The manufacturer provides ranibizumab with the discount agreed in the patient access scheme revised in the context of this appraisal.

People currently receiving ranibizumab for treating visual impairment due to diabetic macular oedema whose disease does not meet the criteria above should be able to continue treatment until they and their clinician consider it appropriate to stop.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Diabetic macular oedema

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Endocrinology

Family Practice

Geriatrics

Internal Medicine

Ophthalmology

Intended Users

Advanced Practice Nurses

Nurses

Optometrists

Physician Assistants

Physicians

Guideline Objective(s)

To assess the clinical effectiveness and cost-effectiveness of ranibizumab for treating diabetic macular oedema

Target Population

Adult diabetic patients with macular oedema

Interventions and Practices Considered

Ranibizumab

Major Outcomes Considered

- Clinical effectiveness
  - Mean best corrected visual acuity (BCVA) change from baseline to month 12
  - Mean BCVA change from baseline to 2 years
  - Improvement in BCVA ≥15 letters
  - Deterioration in BCVA ≥10 letters
  - Mean number of intravitreal injections
  - Median number of laser treatments

- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for technology appraisal 237 was prepared by Aberdeen Health Technology Assessment (HTA) Group (see the "Availability of Companion Documents" field). The ERG report for this appraisal, TA274 Ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237), was prepared by McMDC and Warwick Evidence (see the "Availability of Companion Documents" field).

Clinical Effectiveness

The manufacturer performed a systematic review of the evidence on the clinical effectiveness of ranibizumab. The review identified 4 randomised controlled trials (RCTs) that included ranibizumab in people with diabetic macular oedema: RESOLVE, RESTORE, READ-2 and DRCR.net. The most important of these were RESTORE (currently unpublished) and DRCR.net. RESTORE was sponsored by the manufacturer, but DRCR.net was an independent trial funded by the United States National Institutes of Health.

Refer to Appendix 1 of the Aberdeen HTA Group ERG report for more information.

Cost-Effectiveness

Economic Literature Review

The manufacturer identified no relevant UK cost-effectiveness studies. The only relevant paper identified was a US study of the cost-effectiveness of laser for diabetic macular oedema (DMO) compared to no treatment.

Number of Source Documents

Clinical Effectiveness

Four randomised controlled trials (RCTs) were included.

Cost Effectiveness

- No published studies met the criteria for inclusion.
- The manufacturer presented an updated economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for technology appraisal 237 was prepared by Aberdeen Health Technology Assessment Group (see the "Availability of Companion Documents" field). The ERG report for this appraisal, TA274 Ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237), was prepared by McMDC and Warwick Evidence (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Summary of the Original ERG's Critique of the Clinical Effectiveness Evidence Submitted

The original ERG had no serious criticisms of the clinical effectiveness material in the manufacturer's submission, which was generally of good quality. It could have been shortened by omitting details of the READ-2 and RESOLVE trials.

The main short-coming was the lack of any comparison with bevacizumab. There are no head-to-head trials, but in those situations, NICE expects an indirect comparison to be attempted. Although bevacizumab is not licensed for intraocular use, it was mentioned in the scope.

Another short-coming at present is a lack of longer-term data on how long patients with diabetic macular oedema (DMO) will need to be treated with ranibizumab. Since the underlying problem of the effects of diabetes on the macula is not removed, long-term maintenance treatment may be necessary.

Cost Effectiveness

Original Economic Model Structure

The manufacturer originally presented a cost utility analysis using a Markov model with quarterly cycles over a 15 year time horizon. This compares ranibizumab monotherapy with laser monotherapy, and ranibizumab combination therapy with laser monotherapy. The main comparison is ranibizumab monotherapy with laser monotherapy.

Transition probability matrices for the first year's four quarterly cycles are drawn from the RESTORE all patient data assuming last value carried forward. Given this, drop-outs do not affect the health-related quality of life (HRQoL) calculations within the modelling. These transition probability matrices are applied to the RESTORE patient population with ≤75 letters at baseline, on the basis that in practice patients with >75 letters will not be treated.

The model assumes that there will be no requirement for treatment with ranibizumab beyond year 2. Patients receive a maximum of 10 ranibizumab injections.

Additional Evidence to the Original Submission Submitted by the Manufacturer during Consultation for NICE Technology Appraisal Guidance 237

In response to consultation on the original appraisal consultation document, the manufacturer submitted a revised cost–utility analysis, addressing reservations the Committee had expressed about the original model and submitted a first patient access scheme. Several consultees and commentators, including patient and professional groups, agreed with the Committee that the manufacturer's original economic model had given an unrealistic representation of likely clinical practice in some respects.

Evidence Review Group's Comments on the Manufacturer's Revised Model during NICE Technology Appraisal Guidance 237

The ERG reviewed the manufacturer's consultation comments and revised economic model. It stated that the revised model's updated estimate of the relative risk of death for people with diabetic macular oedema compared with the general population (relative risk 2.45) was reasonable. It agreed with the manufacturer that this figure may be an overestimate of the true additional hazard associated with diabetic macular oedema, but emphasised that it was a more realistic figure than that used in the original model.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions on Cost-Effectiveness

Availability and Nature of the Evidence

When it reviewed the manufacturer's revised model submitted in the National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance 237, the Committee concluded that the model did not reflect likely clinical practice in at least 6 respects. The manufacturer addressed these issues in its rapid review submission, and offered a revised patient access scheme.

Uncertainties around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee was aware that the manufacturer's base-case model produced an incremental cost-effectiveness ratio (ICER) of £21,200 per quality-adjusted life-year (QALY) gained for treating both eyes by multiplying the ICER for the better-seeing eye model by a factor of 1.5. The Committee agreed that this ICER was from a model that relied on a more plausible set of assumptions than those used in the manufacturer's original submission for NICE technology appraisal guidance 237. However, the Committee also acknowledged the Evidence Review Group (ERG)'s technically more comprehensive approach of accounting for treatment in both eyes explored by the ERG and noted that the manufacturer acknowledged the advantages of this approach. The Committee noted that this approach was subsequently adopted by the manufacturer in its response to the rapid review appraisal consultation document and led to ICERs in the range of £24,600 to £31,600 per quality-adjusted life-year (QALY) gained depending on the utility values used in the model for the Committee's preferred analysis. The Committee agreed that these ICERs would increase if the model accounted for people needing more than 4 treatments with ranibizumab beyond the third year, if people who had laser photocoagulation maintained any improvements in vision after treatment longer than people treated with ranibizumab, and if the model better reflected the population with poorer glycaemic control seen in routine clinical practice.

Incorporation of Health-Related Quality-of-Life Benefits and Utility Values

The Committee concluded that there was uncertainty about which utility data were most appropriate to include in the model. However, the Committee agreed that, in the absence of further evidence, it was reasonable to assume that the range of utility values would probably lie somewhere in between those estimated from the Czoski-Murray and Brown studies.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost-Effective?

The Committee concluded that the manufacturer had provided robust evidence demonstrating a subgroup effect in favour of people with thicker retinas. The Committee concluded that the most plausible ICER for the treatment of all people with diabetic macular oedema was likely to be above £30,000 per QALY gained, and that it therefore could not recommend ranibizumab as an effective use of National Health Service (NHS) resources. The Committee concluded that the most plausible ICER for the subgroup of people with thicker retinas was likely to be higher than the manufacturer's estimate, but would be under £25,000 per QALY gained.

What Are the Key Drivers of Cost-Effectiveness?

The Committee concluded that the cost-effectiveness results were driven by the manufacturer's assumptions about: the need to treat both eyes of people with diabetic macular oedema, the utility associated with changes in vision of the treated eye, likely frequency of ranibizumab injections, the expected duration of benefit from ranibizumab treatment, the number of treatment visits and monitoring visits needed, and the generalisability of the economic evidence, especially about glycaemic control in the treated population.

Most Likely Cost-Effectiveness Estimate (Given as an ICER)

The Committee concluded that the most plausible ICER for the treatment of all people with diabetic macular oedema was likely to be above £30,000 per QALY gained, and that it therefore could not recommend ranibizumab as an effective use of National Health Service (NHS) resources.

The Committee concluded that the most plausible ICER for the subgroup of people with thicker retinas was likely to be higher than the manufacturer's estimate, but would be under £25,000 per QALY gained.

See Sections 3 and 4 of the original guideline document for details of the economic analysis provided by the manufacturer, the Evidence Review Group comments, and the Appraisal Committee considerations.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD) and were provided with the opportunity to appeal against the final appraisal determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated for each recommendation.

The Appraisal Committee considered clinical and cost-effectiveness evidence and a review of this submission by the Evidence Review Group. For clinical effectiveness, two randomised controlled trials were the main source of evidence. For cost-effectiveness, the manufacturer's model was considered.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of ranibizumab for treating diabetic macular oedema

Potential Harms

Adverse reactions of treatment are mostly limited to the eye. Those commonly reported in clinical trials include vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, sensation of a foreign body in the eye, increased production of tears, blepharitis, dry eye, ocular hyperaemia, itching of the eye and increased intraocular pressure. Nasopharyngitis, arthralgia and headaches are also reported as common adverse reactions.

For full details of adverse reactions and contraindications, see the summary of product characteristics available at http://emc.medicines.org.uk/.

Contraindications

Contraindications

Contraindications to ranibizumab include known hypersensitivity to the active substance or to any of its excipients, active or suspected ocular or periocular infections and active severe intraocular inflammation.

For full details of adverse reactions and contraindications, see the summary of product characteristics available at http://emc.medicines.org.uk/.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Clinical Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the National Health Service (NHS) in England and Wales on implementing National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- The technology in this appraisal may not be the only treatment for diabetic macular oedema recommended in NICE guidance, or otherwise available in the NHS. Therefore, if a NICE technology appraisal recommends use of a technology, it is as an option for the treatment of a disease or condition. This means that the technology should be available for a patient who meets the clinical criteria set out in the guidance, subject to the clinical judgement of the treating clinician. The NHS must provide funding and resources when the clinician concludes and the patient agrees that the recommended technology is the most appropriate to use, based on a discussion of all available treatments.
- The Department of Health and the manufacturer have agreed that ranibizumab will be available to the NHS with a patient access scheme which makes ranibizumab available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to Novartis Pharmaceuticals UK Commercial Operations Team on 01276 698717 or Commercial.Team@novartis.com.
- NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on the NICE website (http://guidance.nice.org.uk/TA274).
    - Costing template and report to estimate the national and local savings and costs associated with implementation
    - Audit support for monitoring local practice

Implementation Tools

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237). London (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Apr. 75 p. (Technology appraisal guidance; no. 274).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Apr

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Clinical Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Clinical Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Royle P, Cummins E, Henderson R, Lois N, Shyangdan D, Waugh N. Ranibizumab for the treatment of diabetic macular oedema: a single technology appraisal. Aberdeen Health Technology Assessment (HTA) Group; 2011. Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health Research Web site .
- Ranibizumab for diabetic macular oedema: report for NICE rapid review. Evidence review group report. McMDC and Warwick Evidence; 2012 Aug. 36 p. Electronic copies: Available in PDF from the National Institute for Health and Clinical Excellence (NICE) Web site .
- Ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237). Costing template. London (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Feb 27. Various p. (Technology appraisal 274). Electronic copies: Available from the NICE Web site .

Patient Resources

The following is available:

- Ranibizumab for diabetic macular oedema. Information for the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Feb. 6 p. (Technology appraisal 274). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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