Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Feb. 48 p. (Technology appraisal guidance; no. 305).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Aflibercept solution for injection is recommended as an option for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion only if the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Visual impairment caused by macular oedema secondary to central retinal vein occlusion

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Ophthalmology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the clinical effectiveness and cost-effectiveness of aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion

Target Population

Adult patients with visual impairment with macular oedema secondary to central retinal vein occlusion

Interventions and Practices Considered

Aflibercept

Major Outcomes Considered

- Clinical effectiveness
  - Proportion of eyes with a gain of 15 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters in best-corrected visual acuity (BCVA) from baseline to week 24
  - Mean change at 24 weeks from baseline in BCVA
  - Central retinal thickness
  - Proportions of patients progressing to ocular neovascularisation
  - Safety parameters
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

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Searches of Unpublished Data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 Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Warwick Evidence, Warwick Medical School and McMDC Ltd. Health & Economics (see the "Availability of Companion Documents" field). See Sections 6 and 10.2 of the manufacturer's submission (see the "Availability of Companion Documents" field) for details on identification and selection of studies.

Clinical Effectiveness

Submitted Clinical Effectiveness Evidence

The evidence on clinical effectiveness comes from two trials, COPERNICUS and GALILEO. Patients in the trials were adults (aged ≥18 years) with visual impairment due to macular oedema (MO) caused by central retinal vein occlusion (CRVO) diagnosed not more than 9 months before study initiation. Mean central retinal thickness (CRT) in all study eyes was ≥250 um using optical coherence tomography (OCT) and patients had an Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) of 73 to 24 letters (20/40 to 20/320) in the study eye. In both trials, aflibercept (2 mg intravitreal injection) was compared against sham injection.

ERG's Comments on Clinical Effectiveness

The Evidence Review Group (ERG) regard the aflibercept trials of being of good quality, and providing good evidence that aflibercept is effective in improving vision after CRVO, with an acceptable safety record. One weakness is that patients were not asked, at the end of the trials, whether they thought they had been allocated to aflibercept or sham.

The ERG had access to a network meta-analysis (NMA) undertaken by an academic group. The results reported in the Bayer submission and those reported by the academic group were similar.

The ERG also had access to an independent systematic review (submitted for publication) of treatment of MO after CRVO and this confirmed that the Bayer submission included all relevant published trials of aflibercept, ranibizumab and dexamethasone.

Cost-effectiveness

ERG Comment on Manufacturer's Review of Cost-effectiveness Evidence

Bayer has appropriately provided adequate description of their cost-effectiveness systematic review including search strategy, inclusion/exclusion criteria and description of included and excluded studies.

Number of Source Documents

Clinical Effectiveness

2 randomised controlled trials and a network analysis

Cost-effectiveness

The manufacturer submitted a *de novo* cost utility 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

Meta-Analysis

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 Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Warwick Evidence, Warwick Medical School and McMDC Ltd. Health & Economics (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Summary and Critique of Submitted Clinical Effectiveness Evidence

Quality of Included Randomised Controlled Trials

The manufacturer presented quality assessment results in their submission. The ERG has used the Cochrane risk of bias score and considers both trials to be of good quality. The ERG wondered if at the end of the trials, patients were asked what treatment they thought they had been allocated to. Were they able to distinguish between an injection into the eye, and the sham of pressure without puncture? Asking them would have provided a useful check on the security of masking. The manufacturer reported during clarification that patients were not asked.

Three groups were defined for analysis. For analysis of primary efficacy data, the full analysis set (FAS) was used. FAS was defined as all randomised patients who received any study medication and had a baseline assessment and at least one efficacy assessment after baseline (analysed as randomised). For safety, a safety population (SAF) was used, defined as all randomised patients who received any study medication (analysed as treated). Lastly, a sensitivity analysis was carried out using a per protocol (PP) population which included all patients in the FAS who received at least five injections of study medication and did not have any major protocol violations or deviations (analysed as treated).

The analysis did not include an intention-to-treat (ITT) analysis. Instead, a FAS was reported. The FAS included all randomised patients who received any study drug and had a baseline and at least one post-baseline assessment, and the difference in numbers between true ITT and FAS were trivial – COPERNICUS ITT 115 aflibercept and 74 sham; FAS 114 and 73. GALILEO ITT 106 and 72; FAS 103 and 68. The ERG regards the FAS as suitable for analysis.

Refer to section 3 of the ERG report (see the "Availability of Companion Documents" field) for a summary and ERG critique of the two trials.

Indirect Comparison

In the absence of a head to head comparison of aflibercept against ranibizumab in central retinal vein occlusion (CRVO), the manufacturer undertook a network meta-analysis (NMA) to assess the effects of the two treatments on visual acuity (VA). The manufacturer carried out a systematic search to find relevant clinical data on ranibizumab given in an as needed (PRN) or 'reactive dosing' regimen. Eight studies were identified on the efficacy and safety of aflibercept, ranibizumab, dexamethasone and bevacizumab. Two studies (CRUISE and ROCC) investigated ranibizumab, two studies (COPERNICUS and GALILEO) aflibercept, two studies dexamethasone (GENEVA 008 and GENEVA 009) and two studies investigated bevacizumab. Bevacizumab was not included in the NMA.

The manufacturer states that because of the cross over design of the COPERNICUS, CRUISE and GENEVA trials at 6 months (24 weeks), the NMA was conducted on 6-month trial data only. Thus, five studies reporting the 6-month results of the trials of interest were included in the NMA.

Critical Assessment of the Manufacturer's NMA

The ERG critically appraised the manufacturer's indirect comparisons using a checklist suggested by Donegan and colleagues.

The ERG found that the methods used by the manufacturer to undertake NMA were appropriate. Adequate description of the trials were given. Baseline characteristics of all the studies were presented and the manufacturer gave appropriate reasons for including these studies. The manufacturer has correctly used the Bayesian approach using WinBUGS to analyse the data. Heterogeneity was also tested appropriately. The findings were also presented correctly.

Cost-effectiveness

The manufacturer developed a *de novo* cost utility model with a four week cycle length and a lifetime horizon. Health states are defined in terms of

15 ETDRS (Early Treatment Diabetic Retinopathy Study) letter wide bands, resulting in five health states for the treated eye and five health states for the fellow eye: 25 health states in total. The model assumes that the best-corrected visual acuity (BCVA) of the fellow eye is constant. The base case assumes one year of treatment.

The initial patient distribution is taken from the pooled COPERNICUS and GALILEO patient level data.

See Section 5 of the ERG report (see the "Availability of Companion Documents" field) for additional discussion of the manufacturer's 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 Care 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

Availability and Nature of Evidence

The Committee considered the manufacturer's economic model and the critique and exploratory analyses performed by the Evidence Review Group (ERG). It accepted the model structure, but was concerned by some of the uncertainties about the assumptions used by the manufacturer.

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

The Committee considered the following uncertainties in the model:

- The assumption that the benefits of treatment at 24 weeks would continue indefinitely
- Not including the relative risk of losing 15 or more letters
- The assumption that the duration of aflibercept treatment was 1 year
- The use of European Quality of Life-5 Dimensions (EQ-5D) data as a source of utility values
- Not including the cost of adverse events
- Not including a stopping rule
- Overestimated administration costs for aflibercept and ranibizumab
- Underestimated costs of blindness

The Committee concluded that these uncertainties were unlikely to change the dominance of aflibercept over ranibizumab.

Incorporation of Health-Related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-Related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The Committee noted that the utility values in the manufacturer's base-case analysis were obtained from the EQ-5D data from GALILEO. The Committee heard from the ERG that using utility values from Czoski-Murray or Brown did not substantially affect the cost-effectiveness estimates of aflibercept compared with ranibizumab.

The Committee was not aware of any substantial benefits of aflibercept over its comparators that were not already captured in the quality-adjusted life year (QALY) estimation in the modelling.

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

None

What Are the Key Drivers of Cost-effectiveness?

The manufacturer's sensitivity analyses showed that the cost-effectiveness of aflibercept was sensitive to changes in the number of ranibizumab injections from 0 to 24 weeks and 25 to 52 weeks, the relative risk of gaining 15 or more letters when comparing aflibercept with ranibizumab, the number of aflibercept injections from 25 to 52 weeks, and the number of monitoring visits for ranibizumab from 0 to 52 weeks.

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

The Committee noted that the manufacturer's base-case analysis showed that aflibercept dominated ranibizumab (that is, it was more effective and less costly), resulting in more QALYs and lower costs. The Committee considered the uncertainties in the manufacturer's model and noted the ERG's exploratory analysis, which resulted in slightly more cost savings with aflibercept. It also noted that aflibercept continued to dominate ranibizumab despite the changes made by the ERG.

The Committee noted that the ERG's exploratory analysis, which included the confidential discount applied to the list price for aflibercept, resulted in an incremental cost-effectiveness ratio (ICER) of £12,300 per QALY gained for aflibercept compared with dexamethasone. The Committee also noted that even using the Brown utilities for the 'better-seeing eye', that is to say, the 'worst case scenario', the ICER was below the top end of the range that would normally be considered a cost-effective use of National Health Service (NHS) resources (£20,000–£30,000 per QALY gained).

See Sections 3 and 4 in the original guideline document for additional information.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organizations 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.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the manufacturer of aflibercept and a review of this submission by the Evidence Review Group (ERG). The main clinical effectiveness evidence came from randomised controlled trials. For cost-effectiveness, the Appraisal Committee considered an economic model submitted by the manufacturer.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion

Potential Harms

Adverse reactions to treatment are mostly limited to the eye. The summary of product characteristics lists the following adverse reactions as common or very common for aflibercept solution for injection for macular oedema secondary to central retinal vein occlusion (CRVO): conjunctival haemorrhage, increased intraocular pressure, eye pain, vitreous detachment, vitreous floaters, increased lacrimation, and ocular hyperaemia.

For full details of adverse reactions, see the summary of product characteristics.

Contraindications

Contraindications

Contraindications for aflibercept solution for injection include hypersensitivity to the active substance or any of its excipients, active or suspected ocular or periocular infection, and active severe intraocular inflammation.

For full details of contraindications, see the summary of product characteristics.

Qualifying Statements

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care 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

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Service (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has macular oedema secondary to central retinal vein occlusion and the doctor responsible for their care thinks that aflibercept is the right treatment, it should be available for use, in line with NICE's recommendations.
- The Department of Health and the manufacturer have agreed that aflibercept will be available to the NHS with a patient access scheme which makes aflibercept 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.
- NICE has developed tools to help organisations put this guidance into practice. These are available on the NICE Web site (see also the "Availability of Companion Documents" field).

Implementation Tools

Mobile Device Resources

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 Care Excellence (NICE). Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Feb. 48 p. (Technology appraisal guidance; no. 305).

Adaptation

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

Date Released

2014 Feb

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 Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

Committee Members: Professor Andrew Stevens (*Chair of Appraisal Committee C*), Professor of Public Health, University of Birmingham; Professor Eugene Milne (*Vice Chair of Appraisal Committee C*), Director for Adult and Older Adult Health and Wellbeing, Public Health England; Dr Andrew Burnett, Formerly Director for Health Improvement and Medical Director, NHS Barnet, London; David Chandler, Lay Member; Gail Coster, Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust; Professor Peter Crome, Honorary Professor, Department of Primary Care and Population Health, University College, London; Dr Greg Fell, Consultant in Public Health, Bradford Metropolitan Borough Council; Dr Wasim Hanif, Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham; Dr Peter Jackson, Clinical Pharmacologist, University of Sheffield; Dr Janice Kohler, Senior Lecturer and Consultant in Paediatric Oncology, Southampton University Hospital Trust; Emily Lam, Lay Member; Dr Nigel Langford, Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary; Dr Allyson Lipp, Principal Lecturer, University of South Wales; Dr Claire McKenna, Research Fellow in Health Economics, University of York; Professor Gary McVeigh, Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital; Dr Grant Maclaine, Formerly – Director, Health Economics and Outcomes Research, Becton, Dickinson and Company, Oxford; Dr Andrea Manca, Health Economist and Senior Research Fellow, University of York; Dr Paul Miller, Director, Payer Evidence, AstraZeneca UK Ltd; Professor Stephen O'Brien, Professor of Haematology, Newcastle University; Alan Rigby, Academic Reader, University of Hull; Professor Peter Selby, Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust; Dr Tim Stokes, Senior Clinical Lecturer, University of Birmingham; Dr Paul Tappenden, Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield; Dr Judith Wardle, Lay Member; Professor Robert Walton, Clinical Professor of Primary

Medical Care, Barts and The London School of Medicine and Dentistry

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.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

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

Availability of Companion Documents

The following are available:

- Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion. Costing statement. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Feb. (Technology appraisal guidance; no. 305). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Shyangdan DS, Cummins E, Clar C, Ford J, Court R, Lois N, Waugh N. Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion – a single technology assessment. Coventry (UK): Warwick Evidence; 2013. 150 p. Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site .
- Bayer. Single technology appraisal (STA). Specification for manufacturer/sponsor submission of evidence. 2012 Jun. 349 p. Electronic copies: Available in PDF from the NICE Web site .

Patient Resources

The following is available:

- Aflibercept injections for sight problems caused by macular oedema from central retinal vein occlusion. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Feb. (Technology appraisal guidance; no. 305). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download as a Kindle or EPUB ebook from the 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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