RNIB supporting blind and partially sighted people

Consultation response

NICE consultation: bevacizumab as a comparator in the appraisal of ranibizumab for the treatment of macular oedema caused by retinal vein occlusion

Response from Royal National Institute of Blind People (RNIB)

We are pleased to have the opportunity to comment on findings from NICE's Decision Support Unit (DSU).

RNIB strongly believes that bevacizumab should not be used as a comparator in the appraisal of ranibizumab for the treatment of RVO.

The following provides general views, followed by specific comments on each of the four areas examined by the DSU, and concludes with final remarks.

General comments

RNIB has always pressed for patient safety to lie at the heart of any decision about drug treatments. We base our assessment of the clinical effectiveness of new treatments on evidence from randomised control trials, as well as guidance from the Royal College of Opthalmologists. As a patient group, RNIB has concerns over the use of bevacizumab in the eye as there are still many question marks over its safety.

Whilst we understand the pressure on the NHS to make cost savings and use cheap unlicensed drugs, this short-term economic perspective threatens to undermine safety and the UK regulatory system for medicines. The use of an unlicensed medication also jeopardises access to new innovative treatments for NHS patients.

NICE guidance has significant influence internationally due to the rigorous processes it uses to assess new medical technologies. Allowing bevacizumab to be used as a comparator in this appraisal sends out the wrong signals. It suggests that NICE is endorsing the use of an

unlicensed medication which ultimately undermines the purpose of NICE and its guidance.

In the NICE guide to the methods of technology appraisal (June 2008) it states that "relevant comparators are identified, with consideration given specifically to routine and best practice in the NHS (including existing NICE guidance) and to the natural history of the condition without suitable treatment". Prescribing bevacizumab cannot be considered best practice when there is a question mark over its safety and when there is a licensed alternative available.

In addition, questions are also being asked over the legality of prescribing bevacizumab for use in the eye. As you know, the routine prescribing of bevacizumab (in the eye) was recently the subject of legal proceedings between SHIPP Cluster and Novartis, the manufacturer of ranibizumab. We understand that Novartis argued that the practice of prescribing bevacizumab is contrary to European Marketing Authorisation requirements which prohibit a product being placed on the market without a marketing authorisation and the exemptions to those requirements were not engaged. Whilst we understand that the legal proceedings are to be settled, this legal issue remains live.

We are also aware of the difficult position both clinicians and patients face with the current use of bevacizumab for the treatment of wet Age-related Macular Degeneration (wAMD) and we do not want this to be escalated further. Currently, some trusts are putting pressure on their clinicians to make cost savings and prescribe bevacizumab instead of the licensed alternative. This puts the clinician in an awkward position and could breach GMC guidance (which requires that, when prescribing a medicine for use outside the terms of its licence, a doctor MUST be satisfied that it would better serve the patient's needs that an appropriately licensed alternative).

Meanwhile, some patients tell us that they have not been fully informed about the unlicensed nature of bevacizumab when they have been prescribed it for wAMD, while others do not want to cost the NHS money and feel under pressure to take an unlicensed alternative.

The use of bevacizumab in this appraisal will only add to the confusion and we call on NICE to remove it as a comparator.

1. Pharmaceutical quality of reformulated bevacizumab

- From our discussions with clinicians we are aware of and agree with the issues highlighted by the DSU report. Compounding and the risk of infection are of great concern to RNIB.

- Other issues including shelf-life and the conditions in which the drug needs to be transported have not been assessed by the DSU. Patients are being put at risk as the preparation of bevacizimab (for use in the eye) is not subject to the same stringent standards as ranibizumab.

2. Use of bevacizumab in the UK

- As mentioned above, in the NICE guide to the methods of technology appraisal (June 2008) it states that "relevant comparators are identified, with consideration given specifically to routine and best practice in the NHS (including existing NICE guidance) and to the natural history of the condition without suitable treatment". However, as NICE has never defined what "routine use" actually means, it makes it difficult for the DSU to draw any conclusions.

- Our research does not align with findings from the DSU (i.e. that few PCTs policies advocate the use of bevacizumab exclusively). From December 2011 to February 2012, we sent FOI requests to all PCTs to ask them whether they were using the licensed NICE approved drug or whether they were using the unlicensed alternative. We had a 99 per cent response rate and found that 74 per cent are using ranibizumab in line with NICE guidance and the remainder are allowing clinicians to use either bevacizumab or ranibizumab. We would like to highlight that a choice policy tells very little about what is going on in practice.

3. Efficacy of bevacizumab in adults with RVO and diabetic macular oedema (DMO)

- We agree with the DSU conclusion that more evidence is needed before valid conclusions can be reached about the efficacy of bevacizumab in patients with RVO. The DSU quite rightly pointed out that the trials it considered used "relatively small sample sizes and relatively short-term follow-up (the longest was 24 weeks) that differed in terms of participants' age, gender distribution and type of RVO". We

would like to highlight that studies looking at different types of RVO should not be compared. Patients can have either central retinal vein occlusion or branch retinal vein occlusion and these diseases are different and affect different patient populations.

- Similarly, we have concerns that the DSU set out to measure the efficacy of bevacizumab in patients with RVO by comparing it to findings from trials looking at the efficacy of bevacizumab in patients with diabetic macular oedema (DMO). This is not good methodology as DMO and RVO are different diseases which affect different groups of patients.

4. Adverse events using bevacizumab in the eye

- As mentioned above, there are still question marks around the safety of bevacizumab for use in the eye. The DSU report stated the need for further research before further conclusions are drawn. We are aware that trials with larger sample sizes are required to really make judgements about patient safety.

- The DSU noted that "head to head comparisons of ranibizumab and bevacizumab (CATT and IVAN trials), when results are meta-analysed, there is a statistically significantly higher rate of 1 or more serious systematic adverse event (RR 1.27, 95% CI 1.09 to 1.47) in the bevacizumab group.

- Since these trials reported in April and May 2012 respectively, there have been other developments including:

    - In August 2012, Professor Usha Chakravarthy from the Royal Victoria Hospital, Belfast (Ireland) posted a safety update on behalf of the IVAN Investigators. It notes increased risk of systemic serious adverse events (not previously associated with with intravitreal injection of anti-VEGF drugs to treat nAMD) among bevacizumab-treated participants in the two trials. It also concludes that such events among bevacizumab-treated participants is unlikely to be due to chance.

    - The European Medicines Agency (EMA) posting an updated label for bevacizumab in September 2012. It now carries a special warning on eye disorders and systemic effects following intravitreal use.

- We call for a regulatory review into the safety of bevacizumab for use in the eye to be carried out by an expert body such as the Medicines and Healthcare products Regulatory Agency (MHRA). We would like the MHRA to set out any conditions of use as it would with any licensed drug. If MHRA approves the use of bevacizumab along with any conditions the full costs would be known. NICE could then determine whether it is cost effective.

- We are also concerned that arrangements for risk management/ pharmacovigilance are inadequate. A national body needs to be identified to take responsibility for risk management and pharmacovigilance to monitor the on going usage of bevacizumab in the eye if it is found to be safe and cost-effective.

Concluding remarks

We strongly oppose the use of bevacizumab as a comparator in the appraisal of ranibizumab for the treatment of RVO.

There are still big questions around its safety for use in the eye; issues with its preparation and storage meaning that quality cannot be guaranteed; and the evidence for the efficacy of bevacizumab in treating RVO patients is not substantial.

Report author: [redacted]
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About us

As the largest organisation of blind and partially sighted people in the UK, RNIB is pleased to have the opportunity to respond to this consultation.

We are a membership organisation with over 10,000 members who are blind, partially sighted or the friends and family of people with sight loss. 80 per cent of our Trustees and Assembly Members are blind or partially sighted. We encourage members to be involved in our work and regularly consult with them on government policy and their ideas for change.

As a campaigning organisation of blind and partially sighted people, we fight for the rights of people with sight loss in each of the UK's countries. Our priorities are to:

1. Stop people losing their sight unnecessarily
2. Support independent living for blind and partially sighted people
3. Create a society that is inclusive of blind and partially sighted people's interests and needs.

We also provide expert knowledge to business and the public sector through consultancy on improving the accessibility of the built environment, technology, products and services.