Bevacizumab (Avastin) for eye conditions

Report of findings from a workshop held at NICE on 13 July 2010

Summary

Written comments on the pre-scoping briefing document were received from all invited stakeholders. The pre-scoping workshop was attended by most stakeholders; regulatory colleagues provided written comments only.

The use of bevacizumab in the eye is considered ‘unlicensed’ rather than ‘off-label’. The pharmaceutical quality of the product when used for eye conditions needs consideration; to use the product for eye conditions it need to be manipulated to produce a formulation of a strength and volume suitable for intravitreal use.

Bevacizumab is regarded an appropriate treatment option for AMD and non-AMD eye conditions. Stakeholders noted that the product was in use for both AMD and non-AMD conditions before ranibizumab was licensed for AMD. Its use in the former now provides a potential opportunity for cost savings where a licensed product is available, and in the latter reflecting clinical practice in the context of no licensed products.

Patients, clinicians and healthcare commissioning groups would benefit from an appraisal, or appraisals, of the clinical and cost effectiveness of intravitreal bevacizumab in eye conditions. However, there are concerns that recommendations on the clinical and cost effectiveness of intravitreal bevacizumab may be interpreted as a guarantee of safety, and without a specific regulatory review of quality and safety of the product this may be misleading.

Furthermore, since an unlicensed product would not have the support of a manufacturer or sponsor, alternative arrangements for risk management / pharmacovigilance would be likely to have to be put in place in order to monitor the safe usage of the product.

Stakeholders discussed the challenges and considered that an appraisal, or appraisals, of the clinical and cost effectiveness of bevacizumab in eye conditions could be feasible if the safety and quality of the product also are, or have been, adequately assessed.

Summary Findings:

- There are clinical and financial reasons why bevacizumab is currently used as an intravitreal injection to treat age-related macular degeneration (AMD) and non-AMD eye conditions. Doing nothing would not improve the current situation which is seen as unsatisfactory for patients.

- The safety and quality of the product that results from serial dilution have not been subject to regulatory review. There is concern that the product might not be manufactured to the standards used for ophthalmic products. It is important to establish what the characteristics of bevacizumab are when it is used at a low dose in an intravitreal injection; particularly concerning dosing.

- Evidence from existing records of intravitreal bevacizumab in clinical use is available and provides relevant information for the patient population in the NHS. Safety concerns should be reviewed as part of, or before an appraisal. The necessary expertise should be enlisted to consider the safety of intravitreal bevacizumab

- If an appraisal resulted in a positive recommendation, the guidance would have to be supported by adequate ongoing safety surveillance.

Introduction

In response to a request from the Department of Health, NICE undertook a consultation exercise on a briefing paper which was designed to provide a basis for discussing the possibility of appraising bevacizumab intravitreal injections to treat eye conditions. To discuss the comments received during consultation, a workshop was held at NICE at which representatives from patient groups, NHS organisations, professional groups, pharmaceutical companies and the Department of Health were present. In total, 26 people attended (see appendix). No representatives from regulatory authorities were present.

At the workshop, stakeholders considered whether there is a need for an appraisal of bevacizumab for eye conditions and whether the absence of a licence prevents an appraisal from being undertaken. To explore the first of these, participants described the reasons why intraocular bevacizumab is currently used. To explore the second of these, a number of considerations relating to the safety of the product were discussed. These included the implications of not having the guarantee of safety that a licence provides; the lack of a company sponsor to co-ordinate safety surveillance; the evidence

expected to be generated from ongoing clinical trials. The need for national guidance and the feasibility of an appraisal was explored.

Will an appraisal add value?

Key points from the discussion on the value of an appraisal of bevacizumab

1. There is a clinical need to appraise bevacizumab intravitreal injections. It is currently regarded as an option in the following circumstances:
    - Where there are no licensed alternatives for non AMD eye conditions.
    - Where ranibizumab is not available to patients with wet AMD because the criteria recommended by NICE in TA155 has not been met and a patient and their clinician wishes to start treatment with a VEGF inhibitor.
    - Where the desired clinical outcomes have not been achieved with ranibizumab in wet AMD.
2. There is a need to investigate the cost-effectiveness and potential cost savings of bevacizumab intravitreal injections compared with existing treatments.
3. There is a need for consistency in the use of intravitreal bevacizumab and to eradicate the variation in access.

Bevacizumab (Avastin, Roche Products Ltd) is licensed as a treatment for cancer. It is a monoclonal antibody which works by inhibiting vascular endothelial growth factor A (VEGF). VEGF is a mediator in the pathogenesis of certain eye conditions, including wet age-related macular degeneration (AMD), diabetic retinopathy and macular oedema secondary to retinal vein occlusions. There is evidence that VEGF inhibitors can improve vision, whereas the main outcome of traditional treatments such as photodynamic therapy for AMD or laser photocoagulation for macular oedema, is to delay deterioration in vision. There are two VEGF inhibitors which are licensed to treat AMD. These two technologies, ranibizumab and pegaptanib, have been appraised by NICE (Technology Appraisal 155, ‘Ranibizumab and pegaptanib for the treatment of wet age-related macular degeneration’). Ranibizumab is recommended as a treatment for wet AMD in restricted circumstances, whilst pegaptanib is not recommended. There are no licensed VEGF inhibitors for the treatment of non-AMD eye indications.

Ophthalmologists at the workshop gave the reasons why bevacizumab might be considered as a treatment option. Although not licensed as a treatment for eye conditions, it is administered in some hospitals in the UK as an intravitreal injection to treat eye conditions where there are no other licensed treatments, or in a minority of wet AMD cases where improvements in vision have not been achieved with ranibizumab. It is also given to patients whose wet AMD does not meet the criteria in TA155, to recover some vision before further deterioration occurs.

Opportunity for cost saving

Commissioning representatives at the workshop explained that whilst ranibizumab is valued for the clinical benefits that it offers, it places strain on healthcare budgets because of its high cost and the large population of people who meet the criteria for treatment in TA155. An application for marketing authorisation has been submitted for ranibizumab as a treatment for other eye indications, including diabetic retinopathy for which patient numbers will be high and further pressure on healthcare resources can be expected. Since bevacizumab costs significantly less than ranibizumab, there is an opportunity to investigate potential cost savings. At the workshop, the manufacturer of ranibizumab offered to be involved in discussions to assist in making ranibizumab more accessible for patients.

Variation in access

Currently there is variation in the willingness of clinicians to use bevacizumab, and in the criteria set by Primary Care Trusts to fund bevacizumab. Access is determined geographically as an indirect result of these reasons.

Does the absence of a licence prevent an appraisal of intravitreal bevacizumab being undertaken?

To explore the implications of appraising an unlicensed product, the discussions at the workshop focused on the risks to patient safety, issues created by the lack of a company sponsor to co-ordinate surveillance activities and the available evidence to provide a level of safety information.

Key points from the discussion on the implications of appraising an unlicensed product

1. The risks to patient safety from using an unlicensed form of bevacizumab cannot be inferred from the existing license information which is based on infusions of bevacizumab at a significantly higher dose.

2. Data on the safety of bevacizumab in AMD and non-AMD eye conditions has been collected where used in clinical practice. This information could form part of the evidence to review the safety of the product.

3. Standards for manufacturing bevacizumab for intravitreal injection (splitting vials) could be agreed to minimise the risk of contamination.

4. Safety management and surveillance is required. This is a co-ordination role that the NHS may be willing to invest in.

5. Ongoing clinical trials do not provide strong comprehensive safety outcome data (as is the case for many regulatory trials) but it is accepted that they will provide evidence for common adverse events.

Risks to patient safety

Bevacizumab is an unlicensed product for eye conditions, but is licensed for other indications. The product requires splitting into vials of a suitable volume for intravitreal injection. This process changes the volume and method of administration and creates an unlicensed product. The known side effects and contraindications have therefore been determined using studies in which bevacizumab has been given in different volumes and using a different route of administration. It is not known whether the same side effects and contraindications may apply to intravitreal injections of bevacizumab.

Stakeholders explained that bevacizumab is known to be associated with an increased risk of stroke in people with cancer. It is designed to stay in the system for 21 days, and may also be associated with systemic toxicity. It is unknown whether these risks would occur in intravitreal use because a regulatory review has not been undertaken. A regulatory application is a complex, lengthy process, in which safety evidence is rigorously assessed by experts. As bevacizumab has not undergone this process, these stakeholders felt that an appraisal would not be feasible.

To challenge this view, other stakeholders highlighted that the known safety risks of bevacizumab relate to it when given in much higher dosages (for example in metastatic colon cancer it is given as 5 mg per kilogram or 10 mg per kilogram of body weight once every 2 weeks or 7.5 mg per kilogram or 15 mg per kilogram of body weight once every 3 weeks). The suggested dosage of intravitreal bevacizumab is 1.25 mg monthly. It is therefore not possible to infer the same risk of stroke or systemic toxicity as the licensed product. Since bevacizumab has been used since 2005, there is some evidence of how it works in AMD and non-AMD related eye conditions. This information should be utilised as part of a safety assessment of low dose bevacizumab.

It was also recognised that all intravitreal injections present risks and that the relative risks should be assessed to understand whether bevacizumab poses a greater risk than other intravitreal injections. Intravitreal triamcinolone, for example, is contraindicated in ocular use and is associated with an increased risk of glaucoma and cataracts but it is sometimes used when there are no other alternatives. Commissioning representatives explained that they have received funding requests for bevacizumab to avoid the use of triamcinolone.

Concerns were also raised about the process through which intravitreal bevacizumab is manufactured. These were: the absence of a central organisation to oversee standards of manufacture and the potential for variation in the techniques of preparing the product.

In response, stakeholders with experience of the current use of intravitreal bevacizumab explained that vials used in the UK are sourced from one institution (Moorfields Eye Hospital) where the relevant expertise is available to ensure the product is not susceptible to contamination[1]. However it was recognised that a standard process for pharmacies should be established to

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[1] Following the workshop, the Director of the HTA programme advised that before the IVAN trial commenced, MHRA sign-off was required in order to provide quality assurance of the product for use in the trial, which was achieved.

Professor Walley further stated that there are currently two centres manufacturing bevacizumab for eye conditions; Moorfields Eye Hospital in London and Royal Liverpool and Broadgreen University Hospitals pharmacy.

In Liverpool, the pharmacy has extensive stability/sterility/particulate data to meet all MHRA requirements for bevacizumab for eyes. They have an active quality assurance process and can currently guarantee a shelf life of 90 days; but only for a single dose, as used in the IVAN study. They are currently developing data for a second, lower dose and could do more if requested (each set of data costs about £15,000 and takes about 8 weeks). The Liverpool pharmacy is selling to the IVAN and other studies. They are producing about 7,000 doses a year and selling at about £50 per dose (as opposed to ranibizumab [Lucentis] at about £750 per dose).

reduce the risk of microbial contamination. Representatives from Roche confirmed that, whilst two batches had been recalled from other countries because of outbreaks of severe inflammation, these had not been associated with splitting vials.

In summary, there are unknown safety risks and it is important to establish what these are when bevacizumab is used at a low dose. To undertake this, data from existing records of intravitreal bevacizumab in clinical use should be utilised.

Lack of company sponsor to co-ordinate surveillance

A regulatory application for a licence for bevacizumab for ocular use has never been made by Roche Products Ltd. At the workshop representatives from Roche provided the historical context to explain that the decision not to develop bevacizumab for ocular use has been due to corporate considerations. Roche's acquisition of the original owner (Genentech) of the bevacizumab molecule occurred after the decision had already been taken to develop bevacizumab as a treatment for cancer separately to the development of ranibizumab as a treatment for eye conditions. Roche confirmed that there are no plans to apply for a licence for bevacizumab as a treatment for eye indications in the near future.

Stakeholders discussed the implications of there being no licence holder for bevacizumab for ocular use. Representatives from pharmaceutical companies presented a case that patient safety would be compromised unless safety management is to be undertaken. This would involve: setting up and maintaining safety registers, tracking the origin of a batch and recalling it in the event of a defect, writing periodic safety reviews, looking for safety signals, and undertaking post marketing surveillance. It was suggested that this would not be possible if the company were not willing to be involved. As a consequence, these stakeholders suggested that an appraisal would not be appropriate.

In response, stakeholders with experience of intravitreal bevacizumab in clinical use gave their views that it would be relatively easy to track a batch because it is a specialist product which is only likely to be made by a few pharmacies. It is not likely to be any more difficult than tracking the manufacturer of a generic drug. Stakeholders also suggested that the role of maintaining safety registers may be something that the NHS could provide the necessary skills to undertake.

As a result of safety management discussions, it was agreed that the feasibility of an appraisal is not compromised although adequate safety monitoring is important and should be considered in parallel with an appraisal.

Availability of relevant evidence

At the workshop, a presentation of the quantity of published and ongoing clinical trials involving bevacizumab was given by Southampton Health Technology Assessment Centre. A total of 224 published or ongoing studies were identified. The most commonly studied eye condition was AMD.

Stakeholders considered that sufficient trial information would be available from the available evidence, and particularly from the ongoing CATT and IVAN trials of bevacizumab compared with ranibizumab. However, concern was expressed that these trials do not have the support of an independent data monitoring committee, and are not powered to detect all adverse events, particularly stroke and sterile endophthalmitis. Other stakeholders provided an alternative view that the risks are low and a trial would need to be unfeasibly large to provide any guarantee of detecting them. It was suggested that this is not uncommon for clinical trials, which are not always able to pick up all safety signals. Safety reporting often occurs after licensing and since there is experience of using intravitreal bevacizumab, some very relevant safety information already exists for the patient population concerned. It was also noted that the IVAN trial will provide pragmatic trial evidence since it is being conducted in patients treated in the NHS.

The outcome of these discussions was to accept that the CATT and IVAN trials are not sufficiently powered to provide strong comprehensive safety outcome data but they will provide evidence for common adverse events. Evidence from published and ongoing clinical trials would be enhanced when combined with incident reporting databases and yellow card information.

Options explored

Stakeholders considered the possible options in the light of previous discussions on patient safety and the availability of evidence. These were:

- Discard the possibility of an appraisal on the grounds that no regulatory review has been undertaken and no company sponsor is available to co-ordinate safety management;

- Recommend the topic for appraisal without any further safety data on the grounds that the risks are already being balanced by clinicians and patients on a case by case basis;

- Investigate the possibility of enlisting the help of the relevant expertise to address the safety concerns and recommend the topic for future appraisal.

Option 1 – discard the possibility of appraisal

Stakeholders in favour of this option presented a case that an appraisal Committee cannot judge either the clinical effectiveness or the cost effectiveness of the technology because the safety of the product is unknown. A number of other stakeholders suggested that doing nothing, and leaving the situation as it currently stands would be to the detriment of many people, including patients, clinicians and healthcare decision makers. These stakeholders emphasised that it is important to distinguish between the absence of a licence because a product is unsafe, and the absence of a licence because a company has not requested one. Since there is some evidence relating to the use of the product and therefore a possibility that safety can be investigated, it was felt that this option was not necessarily the most appropriate.

Option 2 – recommend the topic for appraisal

Stakeholders considered that proceeding to an appraisal would mean overlooking the absence of a regulatory review and the level of safety that a licence provides. Dismissing this aspect, and proceeding to appraisal would undermine the regulator and have implications for other drugs. Some stakeholders felt that this would not be consistent with the ethos of the NHS which holds patient safety as one of its core values. Therefore this option was not considered appropriate.

Option 3 – investigate the possibility of gaining regulatory expertise to address safety concerns with the intention of recommending the topic for appraisal

A third option was discussed in which it was suggested that the Department of Health and NICE should explore the possibility of involving the relevant skills from a regulatory organisation, such as the MHRA, as part of an appraisal.

The basis for suggesting this option was that it may be possible to form a conclusion on the safety of intravitreal bevacizumab using the information that is currently available. Whilst some stakeholders thought that only a clinical trial designed for the purposes of a licence application would suffice, others suggested that the volume of clinical trial evidence could be combined with reports of intravitreal bevacizumab in clinical practice to provide more data than is usually available for a regulatory submission. Safety data is often only collected after licensing, however bevacizumab has been in use for some years and therefore, informally at least, safety monitoring is already being undertaken. Furthermore, the available data relates to patients from the NHS, and should not be considered less informative than a clinical trial which sometimes involve patients with different demographics.

Stakeholders discussed the timing of a safety review relative to any proposed appraisal. It was recognised that even if an appraisal were to be recommended, it would be unlikely to happen sooner than the anticipated reporting dates for the ongoing IVAN and CATT trials. A full regulatory review process could take a number of years, however this may not be necessary and should be subject to further discussions between NICE, the Department of Health and a regulatory body such as the MHRA. There was mixed opinion on whether a safety review should occur before or as part of an appraisal, however it was difficult to conclude on this point without first discussing the possible options with the relevant organisations.

Conclusion

There is support for an appraisal of intravitreal bevacizumab for eye conditions. Stakeholders agreed that an appraisal would need to be conditional on, or incorporate the assessment of, the safety and quality of intravitreal bevacizumab by a regulatory body or through the involvement of regulatory expertise. It was suggested that options for commissioning the relevant skills and expertise for this purpose be explored. Arrangements for safety monitoring / pharmacovigilance will need to be explored.

Appendix – Workshop participant list

1. Allergan Ltd UK x 2 representatives
2. Bradford and Airedale Primary Care Trust (BA PCT) x 1 representative
3. Bristol-Myers Squibb Pharmaceuticals Ltd (BMS) x 1 representative
4. Department of Health (DOH) x 2 representatives
5. Macular Disease Society x 2 representatives
6. Moorfields Eye Hospital x 2 representatives
7. NHS Bristol x 1 representative
8. NHS Quality Improvement Scotland x 1 representative
9. Novartis Pharmaceuticals (UK) Ltd x 2 representatives
10. Pfizer Ltd x 2 representatives
11. Roche Pharmaceuticals x 2 representatives
12. Royal College of Nursing (RCN) x 2 representatives
13. Royal College of Ophthalmologists (RCOPHTH) x 2 representatives
14. Royal National Institute of Blind People (RNIB) x 2 representatives
15. Southampton Health Technology Assessment Centre x 2 representatives
16. NICE representatives x 6