19th Expert Committee on The Selection and Use of Essential Medicines

April 8-12 2013

Expert peer review on application for inclusion of bevacizumab under ophthalmological preparations

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included

   No (if no, please provide reference and information)


   The intravitreal use of bevacizumab in exudative age related macular degeneration (AMD) should be considered an off-label and unlicensed use. This medicine has not been licensed for this indication in any country. However, there is now sufficient data to establish its efficacy in this condition based on published data. The Comparison of AMD Treatments Trials (CATT) has also proved this (reference No.3 in the review).

   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   The efficacy of bevacizumab is comparable to the agent that has been licensed for its use – ranibizumab. The optimal dose and frequency of treatment have not been worked out though the suggested dose is 1.25 mg given by the intravitreous route on a monthly basis.

   c. Please provide any additional relevant information with reference

   The main issue here is that the licensed medicine (ranibizumab) is very expensive whereas bevacizumab is not since a single vial can be used for multiple doses which enables ophthalmologists to use a single vial for many patients. The volume used per patient is 0.05 ml. In some countries such as the U.K. bevacizumab is split into smaller vials of the required volume prior to use. This process changes the volume and creates an unlicensed product* which may not adhere to any standards of quality and stability.

*Bevacizumab (Avastin) for eye conditions: Report of findings from a workshop held at NICE on 13 July 2010 from http://www.nice.org.uk/media/ac2/3c/bevacizumabeyconditionsprescopingreport.pdf

2. Assessment of safety
   a. Have all relevant studies on safety been included

      No (if no, please provide reference and information)


   The study concluded that safety data from properly designed randomized controlled trials for bevacizumab are not available.
b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

Safety data from postmarketing surveillance for bevacizumab are not available as it is not licensed for this use. The problem with off-label and unlicensed use is that proper monitoring of adverse reactions in a planned manner are not undertaken as is usually done for regulatory purposes. As a result, though the medicine does not seem to have any obvious adverse effects on the eye as well as any of the systemic adverse effects expected from it (as it occurs when used for colon cancer) we must keep in mind that the reported clinical trials on AMD have not been designed to pick up rare adverse effects.

c. Please provide any additional relevant information with reference


The use of an unlicensed medicinal product, when a suitable licensed alternative (ranibizumab) is available, puts prescribing physicians at risk of liability if safety issues arise. Emerging clinical evidence suggests safety differences exist between ranibizumab and bevacizumab as found in the CATT trial.

Recommendations on the clinical and cost effectiveness of intravitreal bevacizumab in macular degeneration should not be interpreted as a guarantee of safety. Unless regulatory review of safety is undertaken, pharmacovigilance data will not be available for evaluation.

3. Assessment of cost and availability
a. Have all relevant data on cost been provided

Yes

b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

Bevacizumab is at least ten times cheaper when compared to ranibizumab, which is licensed for this indication.

c. Please provide any additional relevant information with reference

Avastin versus Lucentis. BMJ 2012; 344 doi: http://dx.doi.org/10.1136/bmj.e3162 (Published 2 May 2012)

d. Is the product available in several low and middle income countries?

It is available in India. The cost of a vial of bevacizumab in India is approximately 100 USD and the cost of a vial of ranibizumab is 900 USD. A single vial of bevacizumab can be used for many patients.

4. Assessment of public health need
a. Please provide the public health need for this product (1-2 sentences)

This medicine is needed for a disease (exudative age related macular degeneration) which affects approximately less than one million people globally. The infrastructure to diagnose and treat these diseases
may not be available in LMIC except in certain specialty eye care centres. Hence the public health need for this product is limited at the moment. However, the low cost of this product makes this treatment option the only one which may be affordable in many of the LMIC.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

No. This product is being used for exudative age related macular degeneration as an off-label use.

5. Are there special requirements for use or training needed for safe/effective use?
If yes, please provide details in 1-2 sentences

Yes. This medicine has to be given by the intravitreal route which requires an ophthalmologist with special training. Also as the medicine does not come in required dosage formulation it has to be pre-packaged into vials or syringes of 1.25mg in 0.5ml. There could be concerns of the sterility of the solution especially when used in LMIC as many patients will be getting this medicine from a single vial.

6. Is the proposed product registered by a stringent regulatory authority?
No - not for intravitreal use.

7. Any other comments

Bevacizumab is used both as off-label (used in an indication, dosage or patient group not specified in the label) and unlicensed (modified in form or strength in a way that has not been assessed or approved, such as splitting a vial into syringes) medicine in age related macular degeneration.

8. What is your recommendation to the committee (please provide the rationale)

I do not recommend the inclusion of bevacizumab into the EML at this point of time as the product is not licensed for intravitreal use. The strength and volume of the formulation which is available (100 mg; 25 mg/ml; 4 ml vial) is not appropriate for intravitreal use and it needs to be split into smaller vials or syringes of 1.25mg/0.05 ml in a sterile manner and stored. The quality and volume of this may vary and standards are not in place. Though the cost is very low (compared to ranibizumab) since many patients typically share one vial (which is how eye care centres are providing this medicine) this alone cannot be the deciding factor in the inclusion of a medicine into the EML.