Expert peer review on application for nAMD (neovascular Age-related Macular Degeneration)

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes ✓ No (if no, please provide reference and information)

   The application coming from the International Council of Ophtalmology quotes only rapidly the largest RCT available (CATT: a large trial with 1200 patients, 300 per arm, comparing bevacizumab and ranibizumab and monthly vs as needed, showing identical efficacy a 1 year and 2 years of follow up) and seems not to pay too much attention in giving a detailed review of 2 drugs that can be considered substantially very similar. It probably assumed that on the basis of available evidence the 2 drugs can be considered equivalent after the recent independent head-to-head trials that have clearly demonstrated beyond any doubts the substantial equivalency of the 2 drugs.

   The application of the International Council of Ophtalmology does not quote another more recent (independent) British study IVAN (300 patients per arm) which showed similar efficacy and safety between the 2 drugs (ranibizumab and bevacizumab) and also for the comparison monthly versus as needed. The IVAN study was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) program (project number 07/36/01) and was recently published in Ophthalmology, July 2012

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

   No other drug is at the moment listed in EML for this indication and only ranibizumab requested a licensed indication whereas avastin/bevacizumab manufacturer did not apply for it.

   Given the very good results of these treatments and the very good quality of available evidence showing similar efficacy of the 2 drugs, bevacizumab 1.25 mg (in 0.05 ml of solution) and ranibizumab 0.50 mg (in 0.05 ml of solution) can be considered equivalent and belonging to the same anti-VEGF class.

   c. Please provide any additional relevant information with reference

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes ✓ No (if no, please provide reference and information)

      Yes, from the point of view of an ordinary application for 2 very similar drugs for which we have available an optimal evidence base with very good direct comparison coming from 2 large independent RCTs. For rare events, such as thrombotic events, estimated in around 1% of patients given the very high age of patients affected by nAMD (in the 2 RCTs mean age was 80 yrs) and the systemic thrombotic events were not higher for bevacizumab compared with to ranibizumab. The hospitalizations were the only outcome (one
among the many secondary outcomes of CATT) which was higher for bevacizumab arm in comparison with ranibizumab but hospitalizations were also higher in the monthly treatment group compared to the as needed group, that is a totally implausible finding (the higher the dose the lower the hospitalization does not seem plausible) due to imbalances in the subgroups. Hospitalization were not even an outcome in the IVAN trial.

The available data coming from large observational studies mostly using record-linkage or pharmacoepidemiology databases have shown very similar adverse event rates between the 2 drugs.

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

As stated in a very recent EMA report (July 2012): "the CHMP agreed that detailed safety information provided from the CATT and IVAN studies is reassuring and no evidence can be provided that bevacizumab is systemically more unsafe than ranibizumab and vice-versa. The CATT study was not powered to detect rare adverse events or to show differences"

c. Please provide any additional relevant information with reference

In order to have a broader view of the difficulties of prescribing intravitreal bevacizumab as an off label indication (in particular in Europe) see also the comprehensive review published in 2012(May 12) in the BMJ "Why using Avastin for eye disease is so difficult. Use of bevacizumab rather than ranibizumab for wet age related macular degeneration has the potential to save substantial sums. But, as Ingrid Torjesen reports, the drug company is fighting to protect its profits"

As for the much easier use of off label prescribing in the US, see the recent NEJM editorial "Off-Label Marketing and the First Amendment" by Marcia M. Boumil (NEJM 10 January 2013).

3. Assessment of cost and availability

a. Have all relevant data on safety provided

   Yes ✓ No (if no, please provide reference and information)

   A short description is given in the application of the huge difference in cost between the 2 drugs since bevacizumab should be prepared (under sterile conditions) into ophtalmic syringes for its use. The difference is in the order of 50-70 times (bevacizumab less expensive than ranibizumab).

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)

   No other drug is listed in EML for nAMD: being the 2 drugs substantially equivalent and being the price 50-70 times higher for ranibizumab in comparison to bevacizumab, this huge difference in price makes one drug affordable and the other drug almost prohibitive in most contexts.

c. Please provide any additional relevant information with reference

   See BMJ review paper quoted above.

   Other important information would be the following:

   - in the US after the CATT study, bevacizuamb is the prevalent and preferred drug for AMD (even if off label given thand given the US legislation)
- the Italian antitrust authority has opened a procedure against Roche and Novartis against free market rules.

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

The product and only this one (bevacizumab) could be available in LMIC given its affordability on conditions of sterile preparation.

4. Assessment of public health need

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

Age-related macular degeneration (AMD) is the leading cause of legal blindness in developed countries and affects a relevant proportion of elderly patients. It is estimated by several epidemiological studies in representative samples of adult or elderly population that in older than 50 years of age the prevalence of neovascular macular degeneration is about 2-3% with a prevalence increasing with age (reaching 7-10% in people >80 year or older).

4b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable


5. Are there special requirements for use or training needed for safe/effective use?

If yes, please provide details in 1-2 sentences

A capacity to perform intravitreal must be available for all available drugs with a need for sterile preparation for bevacizumab. Also ranibizumab is available in vial and not in prefilled syringe.

6. Is the proposed product registered by a stringent regulatory authority?

   Yes  No ✓

The reason for the fact that only ranibizumab manufacturer requested the approval for this AMD indication whereas the manufacturer of bevacizumab (AVASTIN) did not submit any application for AMD and for this reason it is to be used the 4 mg vial for oncologic use.

7. Any other comments

It would be very important to have bevacizumab in the EML (as an off label drug) because it would underscore the medical reasons supporting this request and its clinical uses.

It would also show that there are just economic reasons for bevacizumab manufacturer for not asking for its approval.

It is probably redundant to add that no regulatory authority has refused the approval but simply that the manufacturer of bevacizumab has decided not to present the request.

For public health reasons and in the interest of patients and health system it would be an important step forward to add bevacizumab in EML on the basis of the available evidence coming from independent publicly funded head-to-head trials showing that the 2 drugs have a substantially overlapping (favourable) benefit-risk profile.
8. What is your recommendation to the committee (please provide the rationale)

The application of introducing bevacizumab for intraocular use for AMD should be strongly supported on the basis of the evidence coming from 2 independent RCTs, respectively funded in the US and in UK.

For both drugs there is an issue of injecting it under sterile conditions

The price of the 2 very similar (anti VEGF) drugs is incredibly different making bevacizumab affordable and ranibuzumab excessively costly.

The fact that only one drug is approved is simply the result of the fact that indications are given under the request of the manufacturer (or marketing authorisation holder) which in this case has been done only by one manufacturer.

There are no medical reasons for refusing the inclusion in EML of bevacizumab in the interest of patients and of public health or as stated by Rosenfeld in his accompanying editorial of CATT trial (NEJM, May 19, 2011) “The CATT results, together with the totality of global experience, support the use of either bevacizumab (Avastin) or ranibizumab (Lucentis) for the treatment of wet AMD” and in a health system perspective: “Health care providers and payers worldwide will now have to justify the cost of using ranibizumab (Lucentis). Regulators in certain countries will be forced to reconsider their policies that make it illegal to use drugs off-label particularly when so many of their citizens cannot afford ranibizumab (Lucentis)”.

A detailed analysis of all studies available regarding the safety of bevacizumab (and ranibizumab) is available as an Appendix.