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Bevacizumab in Eye Conditions: Issues related to Quality, Use, Efficacy and Safety.

Thank you for the opportunity to comment on the above report by the Decision Support Unit. The DSU literature review is comprehensive. They have captured key information about efficacy and safety.

We particularly welcomed the report as the use of bevacizumab for AMD and other macular disease has, and continues to be an issue for commissioners and providers across the UK.

NHS patients have been recruited into IVAN, and a significant number are being recruited into TANDEM. Commissioners have included financial incentives within contracts with acute providers to encourage recruitment into TANDEM. These studies have been established and are supported by NHS commissioners, specifically because of the unusual circumstance where the manufacturer has no incentive to undertake or support these trials, due to its competing commercial interest in its licensed product, ranibizumab.

Licensing:
The DSU report explains clearly the fact that bevacizumab does not have a license for ocular use (pg7). However, it would have been helpful to explain the context i.e. that Roche/Genentech has commercial interest in both products. The DSU report would be more accurate if it explained that ranibizumab is promoted in the UK by Novartis under license from Roche. This is why there now exists the unusual situation where an alternative drug to ranibizumab remains unlicensed.

Supply and Safety:
Section 2 of the report addresses some of the production issues associated with the aliquoting of bevacizumab into doses suitable for intravitreal injection.

Whilst it is true that there is potential for greater risk of contamination of the product, the report does not make it clear that the risk can be greatly reduced by doing this in an aseptic pharmacy unit, which has a license for undertaking this work. It is worth noting that aliquoting drugs is not an unusual practice and is certainly not unique to intravitreal injections (e.g. intrathecal chemotherapy drugs are a common example of the role of an aseptic wholesale unit). We would certainly not support the supply of bevacizumab from any source other than Moorfields and Liverpool units, as this does present an unacceptable and avoidable risk of contamination.

The risk of endopthalmitis associated with bevacizumab is not clearly reported. The report needs to make a clear distinction between the incidence of endopthalmitis where the bevacizumab was aliquoted in a local office and administered in a non-sterile setting, and the incidence of infections where the aliquots were supplied by a licensed aseptic wholesale supplier and administered in a clean room/sterile setting. The US examples on page 10 and 11 included local office repackaging of bevacizumab and administration in non-sterile conditions.

Additionally, endopthalmitis has been reported with intravitreal ranibizumab. This highlights that there is a risk of infection with intravitreal injection. It is not clear from the DSU report how the incidence of endopthalmitis associated with IVB (from a licensed aseptic supplier, administered in a clean room) compares with the incidence of endopthalmitis associated with intravitreal ranibizumab. There are a number of confounding issues. It seems from CATT and IVAN ((pg 65, Fig 19) that where the supply chain and administration is quality assured that there is no significant difference in adverse events between bevacizumab and ranibizumab intravitreal treatment.

Usage:
We are not surprised that few PCTs have published formal commissioning policies about bevacizumab on their website. Some commissioners part fund TANDEM and incentivise providers to recruit patients to TANDEM and IVAN. However, they may not have a formal policy stating this. Commissioners generally don't have formal policies for each and every condition or drug.

In addition, since December 2012, commissioners have been very aware of the legal action being taken by Novartis against SHIP PCTs for their policy on the option of bevacizumab as an alternative to ranibizumab. Therefore the information secured by the DSU is skewed by both the existence of the already published technology appraisal guidance on ranibizumab for wet AMD and the knowledge of the judicial review underway at the time of the DSU search for policies.

A number of PCTs (collectively) in England have been reviewing of the evidence of effectiveness of ranibizumab and bevacizumab for the treatment of diabetic macular oedema and retinal vein occlusion, where NICE has not recommended the use of ranibizumab for these indications. Local discussions with ophthalmologists indicate that many would prefer to use bevacizumab rather than ranibizumab for these indications. Legal and regulatory concerns are the barriers to greater use of bevacizumab rather than issues of efficacy or safety.

The DSU report is a large and comprehensive review which does address the issues they were asked to address by NICE.

We do wonder however whether they could have got a better response rate from their survey of ophthalmologists. Sending a questionnaire in the summer with a very short time to respond is unlikely to elicit a large response. With a response rate of 17% the survey results are surely meaningless. They could have approached directly those consultants that are participating in IVAN or TANDEM, or followed up non-responders directly?

Yours sincerely

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On behalf of the CSAS Steering Group

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