Novartis response to the August 2012 report by the Decision Support Unit ("the DSU") – Bevacizumab in eye conditions: Issues related to quality, use, efficacy and safety ("the DSU Report")

Executive Summary

Novartis has maintained consistently throughout this appraisal that unlicensed bevacizumab is not a valid comparator for ranibizumab in the treatment of patients with visual impairment (VI) due to macular oedema secondary to retinal vein occlusion (RVO). Furthermore, the DSU Report supports the conclusions drawn previously by Novartis, and raised since NICE's scoping of this appraisal, that the available evidence on the safety, efficacy and quality of unlicensed bevacizumab is inadequate to draw any robust conclusions. Our key comments on the DSU report are summarised as follows:

Quality

- There are issues relating to product quality that the DSU did not address in its report and as such their assessment contains major omissions and flaws:
    - Bevacizumab currently only meets intravenous quality standards, rather than the more stringent ophthalmic standards regarding sub-visible particle matter and endotoxin levels. The implications of this on quality and safety have not been addressed.
    - The presence of sub-visible particles and/or silicon oil is critical in the case of intravitreal injection (accumulation in the eye, leading to potential for severe intraocular inflammation). Neither parameter appears to have been considered in the DSU's assessment.
    - No data are presented to consider the quality of the product after repackaging from a microbiological as well as a physiochemical point of view. Nor is the compatibility of the solution with the primary packaging considered.
    - There has been no examination of the shelf-life setting of repackaged bevacizumab, and the impact on safety and quality.
- Whilst the DSU recognised that the risk of sterile endophthalmitis increases with repackaged bevacizumab resulting in outbreaks (including one associated with the largest UK supplier), additional published evidence regarding the level of risk to patients was omitted. A recent chart review reported that individuals treated with intravitreal bevacizumab (IVB) were 12 times more likely to develop severe intraocular inflammation than those who received ranibizumab.[1]
- The DSU did not appear to seek any definition or protocol for compounding and administration procedures. The DSU survey reports that there is substantial supply of bevacizumab in the UK from 'non-specials' manufacturers (nearly 30%) and that local compounding of bevacizumab has been associated with a higher risk of infection.

- Thus, the variation in the quality of the product means that the evidence for safety and efficacy from the unlicensed use of bevacizumab is not generalisable from the clinical trial setting to that of routine clinical practice.

Safety

- Novartis is reassured that the DSU reached a similar conclusion regarding the fact that there is insufficient evidence to fully evaluate the safety profile of bevacizumab.
- In the pooled analysis of the IVAN[2] and CATT[3] studies, the incidence of any serious systemic adverse event was significantly higher in the bevacizumab group compared to the ranibizumab group. The Technology Appraisal Committee (TAC) should be made aware that the Data Safety and Monitoring Committee of the IVAN study considered these findings to be real, not due to chance, and to be serious enough to warrant informing patients and offering them the opportunity to exit the trial early.[4, 5] This highlights that there is a significant safety signal with IVB, even within the controlled clinical trial setting.
- It should also be highlighted to the TAC that the updated bevacizumab EMA Summary of Product Characteristics now warns of the local and systemic safety risk of unlicensed IVB use and their theoretical association with the known suppression of systemic VEGF levels following IVB use.[6]

Efficacy

- Novartis is also reassured that the DSU confirms previous conclusions that the clinical evidence for IVB in RVO is limited and that no reliable conclusion can be drawn regarding its efficacy.
- The clinical evidence in diabetic macular oedema (DMO) presented in the report is irrelevant to the RVO appraisal; DMO and RVO are different diseases in different patient populations.
- It is well established that RCT evidence for one type of RVO (BRVO) cannot be extrapolated to the other (CRVO).
- The quality of IVB will vary across studies, and by source, and as such no conclusions can be drawn about its efficacy in routine practice.
- Drawing on the experience of the recent GSK appeal in the appraisal of belimumab for lupus, there are obvious concerns regarding recommendations made on the basis of limited clinical evidence for comparators.

Use

- The DSU conducted an internet search of publicly available documents from NHS commissioners on the use of bevacizumab. The methodology for this search is questionable and reliable conclusions cannot be drawn from the commissioning documents identified in the DSU Report.

- The DSU survey of NHS consultant ophthalmologists is unreliable as no actual patient numbers were recorded, it was not reported how many of the consultants who responded to the survey worked in the same centre, and it may not reflect a likely trend towards the use of dexamethasone intravitreal implant for RVO following NICE recommendation of this agent.
- The DSU does not conclude that IVB is 'routinely' used or 'best practice' in the NHS, or provide a definition of these terms in the context of its findings.

Other considerations and wider ramifications

- The DSU Report highlights that "it is the view of the MHRA that ocular use of bevacizumab constitutes an unlicensed as opposed to off-label use because of the manipulation of the licensed product." Therefore we believe that bevacizumab for intravitreal use falls outside the definition of a comparator under NICE's procedures.
- The use of IVB does not represent best practice. The intravitreal administration of a formulation which has undergone no regulatory scrutiny, in circumstances where the data supporting such use are very limited, cannot be viewed as "best practice", particularly in circumstances where alternative treatments, tested and authorised for such use, are available.
- The use of an unlicensed comparator is inconsistent with the medicines licensing regimen and undermines the protection to public health provided by that regimen.
- On 22 December 2011, Novartis issued Judicial Review proceedings to seek a review of a decision by the Southampton, Hampshire, Isle of Wight, Portsmouth ("SHIP") Primary Care Trust Cluster to issue a policy recommending the use of bevacizumab to treat patients with wet AMD. At a Board meeting on 24 September 2012, the SHIP Cluster Board made the following statement:

  "The Cluster Board formally confirms that the Policy decision concerning the use of bevacizumab for Wet Age Related Macular Degeneration, taken on 27 September 2011, has been revoked. There will be no policy relating to the commissioning of bevacizumab for wet AMD. The NICE TA155 (as updated in May 2012) is being followed by the SHIP PCT Cluster and, accordingly, funding for Lucentis is being made available in the SHIP PCT Cluster. The PCTs will not encourage the use of any other treatment for wet AMD."

- The European Court of Justice has ruled in a case involving Poland that financial considerations cannot justify the placing on the market of unlicensed medicines where licensed alternatives exist.[7] Accordingly, the reformulation of bevacizumab for the purposes of administration to NHS patients for the treatment of eye conditions is unlawful and the reliance on a comparison with such unlicensed formulations for the purposes of NICE Guidance is inappropriate and improper.

- Any recommendation based on a comparison with an unlicensed product represents some endorsement by NICE of the unlicensed treatment, even if no explicit recommendation is made.
- The DSU Report acknowledges the manufacture of bevacizumab as a "special". However, it does not assess whether the supply by Moorfields and Liverpool meets the specials requirements – without this assessment, NICE would appear to be indicating that all use can be considered whether or not that use is legitimate use.

Introduction

NICE requested the DSU to consider four questions of potential relevance to the consideration of IVB as a comparator in appraisals of licensed therapies for RVO. The four questions are summarised below:

1) What evidence is there relating to the pharmaceutical **quality** of reformulated bevacizumab as used in eye conditions in general?

2) How widespread is IVB **use** in the UK?

3) What is the evidence for **efficacy** of IVB in adults with RVO and DMO specifically?

4) What evidence is there regarding **adverse events** for IVB in eye conditions in general?

Novartis strongly believes and has consistently maintained throughout this appraisal that bevacizumab is not a valid or appropriate comparator for ranibizumab in the treatment of patients with visual impairment due to macular oedema secondary to RVO. It is noted that, notwithstanding the commissioning by NICE of the DSU Report in the context of assessing the use of bevacizumab as a comparator in RVO, the DSU's additional work was not restricted to considering bevacizumab solely in RVO, but considered bevacizumab in all eye conditions. However, the Novartis response to the DSU Report is limited to points relevant to RVO and this appraisal only.

We set out our comments to the DSU report below.

1. Quality

1.1 Pharmacological issues relating to quality were omitted in the DSU's assessment

There are issues of quality that the DSU Report does not mention. This is of particular concern given that these quality issues influence ocular safety and variation in quality means that the results of clinical trials may not be generalisable to routine practice.

Novartis believes that the DSU has not done a complete review and appraisal of the evidence pertaining to the quality of reformulated bevacizumab as several key papers have not been assessed or commented on. In addition the DSU Report does not seem to have acknowledged the recent NHS Quality Assurance Advice notes that have been circulated to Chief Pharmacists. [12]

Given the limited and incomplete quality assessment undertaken by the DSU, there is clearly insufficient evidence on which to draw any conclusions with regards to the quality of bevacizumab. Indeed we believe more questions are raised, than answers provided.

Novartis believes that the quality assessment undertaken by the DSU is severely lacking with major omissions and flaws for the following reasons:

- The 'Quality' section of the DSU Report does not mention that bevacizumab currently only meets intravenous quality standards for particulate matter, rather than the more stringent ophthalmic standards (Ph. Eur. 2.9.19./ USP 788, and USP 789 respectively) that specify the maximum average number of sub-visible particles in the drug solution and define significantly lower total particle numbers for the intravitreal route of administration.

Table 1: Light obscuration test particle count according to the physical test applied

	Diameter	
Number of particles according to	≥ 10 µm	≥ 25 µm
USP 788 & Ph Eur method 2.9.19.	6000/ container corresponding to 1500/ mL in the case of 4 mL Avastin vial	600/ container corresponding to 150/ mL in the case of 4 mL Avastin vial
USP 789	50/ mL	5/ mL

- The level of sub-visible particles in repackaged bevacizumab was not discussed in the DSU Report. In a recent study from the UK where samples from five suppliers were analysed for particle density, it was found that a significant difference in sub-visible particle density was observed between bevacizumab batches from the different suppliers on Day 1 ($p < 0.001$).[8] An increase in sub-visible particle density was observed between Day 1 and 14 for repackaged bevacizumab from all suppliers (all $p < 0.05$), but not the reference compound.[8] The study results indicate that the quality of bevacizumab repackaged into pre-filled plastic syringes is variable among the different compounding pharmacies in the UK. Furthermore, particle density may increase with storage in repackaged syringes. The impact of these findings on the safety and efficacy of IVB is unknown.
- Kahook et al 2010 also analysed repackaged bevacizumab syringes obtained from three different compounding pharmacies and found that the repackaging process may lead to deterioration on the quality of the drug with an increasing amount of particulate matter over time. This might be linked to an increased risk of raised intraocular pressure (IOP) and also potentially sterile endophthalmitis.[9]
- The quality section of the DSU does not specify the endotoxin levels of bevacizumab solution. As the eye immune system is weak, the endotoxin limit requirement may be reduced in the case of ophthalmics. As a consequence, the endotoxin limit may not be based on the limits for parenteral administrated products as recommended in the new FDA guidance for industry on pyrogen and endotoxins testing.[10]

- No data are presented to assess the quality of bevacizumab solution repackaged in pre-filled syringes from a physiochemical as well as a microbiological point of view. Stability of antibodies contained in pre-filled syringes may be compromised by the presence of traces of silicon oil or metals coming from siliconised syringe barrel and needle.
- There is limited data on the longer-term stability (physicochemical and microbial) or shelf-life of repackaged bevacizumab, or how it is affected by mechanical stress such as that which occurs during transportation, and by freeze-thawing as can occur during cold-chain distribution.[11, 12]
- No compounding and administration protocols are reported for intraocular administration of bevacizumab. The compounding and administration of bevacizumab solution have only been assessed for intravenous infusion.
- The quality of repackaged bevacizumab solution may be heterogeneous due to the absence of a defined repackaging procedure. This risk is increased by the multiple compounding pharmacies. Therefore no conclusions can be drawn about safety or efficacy because of this fundamental heterogeneity.

1.2 Issues of quality related to local compounding

According to the survey of consultant ophthalmologists conducted by the DSU nearly 30% of clinicians reported using bevacizumab that is supplied by means other than the licensed "specials" suppliers, Moorfields Pharmaceuticals and Liverpool and Broadgreen Hospitals trust (~10% from local pharmacies, ~11% from other sources and ~8% unknown; Figure 1, DSU Report). The DSU state that "some argue that the risks of infection are greater when local pharmacists perform this compounding and this should therefore be avoided" (p.81).

There have been serious adverse events relating to infection due to local compounding of bevacizumab for intravitreal use in the US, as reported by the DSU (pg.10). However, further case series of infectious endophthalmitis due to local compounding have also been reported in Germany and Korea, which were not identified by the DSU.[13]

Further safety issues relating to IVB use are described in the 'Safety' section below.

1.3 Sterile endophthalmitis

Sterile endophthalmitis is a recognised concern with IVB as it was not designed for use in the eye. The DSU Report states that "there were 25 reports of signs and symptoms consistent with sterile endophthalmitis or uveitis suspected to be due to bevacizumab supplied by Moorfields in February 2012 which prompted a recall of several batches and a suspension of production as a precaution" (pg. 11). The DSU Report highlights that despite Moorfields holding a "specials" licence and being the largest supplier of IVB to the NHS, repackaging bevacizumab poses risks due to sterile endophthalmitis regardless of where the compounding is performed (i.e. "specials" suppliers vs. local pharmacies).

However, no attempt was made by the DSU to further elucidate or quantify this risk using the published literature. Sharma et al (2012) conducted a retrospective cohort study in order to compare the rate of serious ocular and systemic adverse effects of intravitreal bevacizumab and ranibizumab in the treatment of a variety of eye diseases. Consecutive series of intravitreal injections of bevacizumab (n = 693) and ranibizumab (n= 891) were analysed. Results showed that patients treated with unlicensed bevacizumab were 12 times more likely to develop severe intraocular inflammation than those who received ranibizumab (odds ratio 11.71; 95% CI 1.5–93).[1]

The DSU report also fails to highlight that outbreaks of sterile endophthalmitis have also been reported in Japan, Australia and Canada.[13]

In the US the Department of Veterans Affairs following the Florida endophthalmitis clusters, now require the use of one Avastin vial per patient, rather than aliquoted bevacizumab in plastic syringes. And in France following two cases of endophthalmitis the Regional Health Agencies have been instructed to ensure that hospitals and clinics do not perform any vial splitting (including with intravenous bevacizumab) for off-label indications when there is a licensed medicine available.

2. Safety

2.1 There is insufficient evidence to fully evaluate the safety profile of bevacizumab

The safety profile of intravitreal bevacizumab, and its subsequent systemic exposure, remains unproven in ophthalmic indications. There has been no regulatory standard clinical programme, which should include pre-clinical and dose-ranging studies, as well as long term post-marketing studies and a pharmacovigilence programme. These concerns were raised in the original Novartis submission to this appraisal and prior to that, in response to the NICE assessment of the feasibility of conducting an appraisal of unlicensed bevacizumab.

We are pleased that the DSU Report has reiterated and highlighted these concerns and also stated that further research is required before conclusions can be made. Only two randomised studies (CATT[3] and IVAN[2]) met the criteria for valid safety data (p.57). However, neither of these studies were powered to identify differences in individual adverse events; the DSU recognised this in their report (p.76). Therefore, given its unlicensed status, bevacizumab should not be considered a comparator until further research confirms its safety for intravitreal use.

Since the quality of IVB preparations differ in clinical practice from that of clinical trials, no meaningful conclusions about the safety of bevacizumab can be made from these studies. For example, the CATT study used single glass vials, manufactured at a single central compounding pharmacy, for each treatment (not plastic syringes from multiple manufacturers) and therefore a low infection risk would be expected.[3, 14] This study therefore does not reflect clinical practice in the NHS and the true risk

of infections. Furthermore, the CATT trial population is not generalisable to the population seen in clinical practice, as people with severe co-morbidities were excluded from the trial.[14]

Thus, the DSU Report supports the conclusion previously made by Novartis that the safety data for use of bevacizumab in ophthalmological indications, including RVO, is too limited to allow a fair comparison to ranibizumab. Furthermore, as wet AMD, DMO and RVO are very different conditions, and the patients with them have very different risk profiles, the risk/benefit profile will vary between them and cannot be generalised across the indications.

2.2 Safety concerns raised by the CATT and IVAN studies have been considered serious by the Data Safety Monitoring Committee

In the pooled analysis of the IVAN[2] and CATT[3] studies, the incidence of serious adverse events at 1 year remained significantly higher for the IVB group compared to the ranibizumab group. The Data Safety Monitoring Committee of the IVAN study considered these findings to be serious, real and not due to chance, and have recently written letters to inform patients enrolled in IVAN, their GPs, and the principal investigators, of these increased risks of IVB and to ask if the patients wish to remain in the trial.[4, 5] This highlights that there is a significant safety concern with IVB, even within the controlled clinical trial setting. This risk must be taken seriously rather than considered, as the DSU Report referred to it, as a "chance statistical finding".

2.3 Bevacizumab label now warns of the safety risk of unlicensed IVB use

Since the DSU undertook its assessment, the manufacturer of bevacizumab has in fact addressed the safety signals with intravitreal use of bevacizumab and the committee should be made aware of the addition of the following special warning to the EMA bevacizumab's summary of product characteristics[6]:

"Eye disorders"

Individual cases and clusters of serious ocular adverse events have been reported following unapproved intravitreal use of Avastin compounded from vials approved for intravenous administration in cancer patients. These events included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these events have resulted in various degrees of visual loss, including permanent blindness.

"Systemic effects following intravitreal use"

A reduction of circulating VEGF concentration has been demonstrated following intravitreal anti-VEGF therapy. Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors, and there is a theoretical risk that these may relate to VEGF inhibition.

Canadian, Australian and Taiwanese labels for bevacizumab have also been changed to include warnings on safety issues associated with intravitreal use.

3. Efficacy

3.1 Clinical evidence is limited in RVO

The DSU Report states that regarding efficacy, "data were limited" (p.82) for RVO, the indication under appraisal, and that "more studies are needed before valid conclusions are reached" (p.49). They also conclude that "due to heterogeneity in the type of RVO (central and branch) and method of assessing BCVA, a meta-analysis was considered inappropriate" (p.47). There are no long term clinical data on the use of IVB in RVO. The longest clinical data are one year in CRVO and 6 months for BRVO. In addition, the limited short term data available draw conflicting conclusions. As Novartis has concluded before, there is insufficient evidence to support a comparison of ranibizumab to bevacizumab and decisions relating to IVB should not be made on the basis of this very limited evidence.

3.2 No reliable conclusion can be drawn from the available clinical evidence in RVO

The efficacy data for IVB reported in the DSU Report are not generalisable to the RVO population seen in clinical practice due to the following reasons:

- With regards to the evidence identified in DMO, it should be noted that although both conditions are related to vascular leakage, DMO and RVO are different diseases in different patient populations and therefore the evidence in DMO is irrelevant to the RVO appraisal.
- Within the RVO indication, BRVO and CRVO are different diseases in different patient groups with different treatment pathways. Therefore the RCT evidence for one type of RVO cannot be extrapolated to the other.
- The quality of bevacizumab syringes across studies will vary, and therefore no conclusions can be drawn about efficacy because of this heterogeneity.

Furthermore, the conclusions made by the DSU regarding the longer term efficacy of bevacizumab in RVO are unfounded, as they infer that longer term data in CRVO overrides the negative data found for BRVO. The fact that these two trials disagree on the efficacy of IVB could mean that: IVB has different efficacy in CRVO compared to BRVO; one or both of the RCTs are poorly designed; or the small population is poorly representative of the wider population. The authors themselves highlight that further investigation is required to elucidate the true efficacy over time and even the DSU comment that further evidence is required to assess the efficacy of IVB in RVO before valid conclusions can be reached.

Drawing on the experience of the recent GlaxoSmithKline ("GSK") appeal against NICE's Final Appraisal Determination on belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus, there are obviously concerns over decisions being made on the basis of poor or insufficient data. Belimumab, a GSK product, has a marketing authorisation as add-on therapy in adult patients with

active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity despite standard therapy. The appraisal which was the subject of the appeal provided advice to the NHS on the use of belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus. In the appraisal, NICE compared belimumab against rituximab, which is being used off-label for the indication in the NHS. The appeal panel upheld GSK's appeal point that NICE's findings in relation to the clinical and cost-effectiveness of belimumab compared with rituximab were unreasonable given the lack of clinical data on the effectiveness of rituximab in the indication and the lack of comparative data on the relative efficacy of the two drugs.[15]

4. Use

4.1 Relevance of NHS Commissioning Documents

Novartis notes that the DSU conducted an internet search of publicly available documents from NHS commissioners on the use of bevacizumab in eye conditions, and would question the relevance of such a search and the commissioning documents identified in the DSU Report, for the following reasons:

- We are not clear that this search was sufficiently structured or systematic, and may therefore result in biased results: it is not clear that there was a search for negative guidance precluding the use of intravitreal bevacizumab; the inclusion/exclusion criteria for policies were unclear which has resulted in the inclusion of policies that are not relevant to the decision problem.
- Most of the documents that supported bevacizumab use did not support it in the indication of visual impairment due to macular oedema secondary to RVO. In many cases where RVO was mentioned, this was for treatment of rubeosis for which ranibizumab is not licensed, and which the current appraisal is not reviewing.
- The commissioning documents identified were reported to have "suggested, recommended or supported the use of bevacizumab in eye conditions". The DSU Report does not give any details as to the content of such documents; bevacizumab may have been recommended as a first line treatment for an indication which already has a licensed and NICE approved treatment. In this scenario, it would not be lawful to recommend an unlicensed treatment where a licensed one exists. From a policy perspective, it is unclear whether NICE are making a statement that it is prepared to consider all use, even where that use is not legitimate.
- The first paragraph on page 24 of the DSU Report states that "bevacizumab was also recommended 'to improve side effects and reduce the use of Lucentis in unspecified settings". As mentioned above, it is not lawful to recommend an unlicensed treatment and encourage its use over that of a licensed treatment.

- The DSU Report states that not all NHS websites were searchable. Out of 145 websites belonging to trusts in England, only 28 contained links to information which "suggested, recommended or supported the use of bevacizumab in eye conditions". Further, Table 1 shows that, out of the 28 websites, only 6 commissioning documents related to RVO. The sample is too small to allow for any reliable conclusions to be drawn from the results of the search.
- A number of the webpages which were identified in the DSU Report had not been updated recently and any policies referred to might well be out-of-date.
- The documents commonly restrict the number of injections of bevacizumab e.g. a limit of 4 treatments per patient. These restrictions must by definition prevent bevacizumab use being routine and best practice, notwithstanding the absence of an accepted dosing regimen.
- Finally the existence of a commissioning policy does not necessarily mean that bevacizumab is being prescribed and used in practice.

4.2 Issues with the DSU survey and conclusions on IVB use

The DSU Report suggests that IVB use is "substantial" across the NHS (p.31), particularly relating to RVO. This conclusion does not seem justified given that results of the survey show that 41.7% of respondents "never" use IVB and 8.6% "hardly ever" use IVB for RVO.

The NICE 2008 Methods Guide states that comparators should include "routine and best practice in the NHS". No definition of what constitutes routine use or best practice is given in the DSU Report. Importantly, the DSU does not conclude that the use they report constitutes "routine" use or whether this represents "best practice".

Importantly, the survey results are not reliable and therefore conclusions based on these are not justifiable. The survey lacks reliability for the following reasons:

- The DSU survey does not report on the actual number of patients being treated with IVB, as there was no question for the consultants on the number of patients that they treat annually. Therefore the conclusions regarding the level of use in the NHS are based on assumptions rather than reliable data.
- It was not reported as to how many of the consultants who responded to the survey worked in the same centre. If multiple consultants from one centre responded to the survey, this would certainly skew the results.
- A survey of a selection of NHS consultant ophthalmologists is open to bias and unless a sufficient sample is taken, the results are unlikely to reflect true use across the NHS. The DSU only sampled 17% of all consultants registered with the Royal College of Ophthalmologists.
- Only consultants were surveyed, which includes many other subspecialists in addition to medical retina clinicians who are the physicians who see these patients routinely in clinical practice.

- Given the rapid fall in use of IVB in wet AMD following the NICE recommendation of licensed ranibizumab, it is likely that IVB use will also have significantly decreased in RVO too due to the recent recommendation (July 2011) of dexamethasone intravitreal implant for this indication. Therefore the DSU survey of NHS consultant ophthalmologists will not have captured the extent of the recent expected uptake of dexamethasone intravitreal implant for the treatment of RVO in this rapidly changing market. Novartis maintain that dexamethasone intravitreal implant is a more relevant comparator than bevacizumab and have previously provided a comparison of ranibizumab versus dexamethasone intravitreal implant.
- There is likely to be a responder bias, whereby those who wish to use unlicensed bevacizumab may be more likely to respond to such a survey, compared to those who do not wish to use it, as respondents will know the purpose of the survey.

4.3 Quantity supplied by main UK manufacturers

Novartis cannot comment on the supply figures reported in section 3.2 of the DSU Report as they have been redacted. This does not allow for full consultation on the DSU report. However, it would be important that these figures are an accurate reflection of routine use in the NHS which would necessitate the exclusion of any supply for clinical trials, use in the private sector and for individual funding requests for compassionate use. Furthermore, it is unknown for what indications this IVB was supplied; we note the use, and potentially the supply, of bevacizumab for rubeotic glaucoma. Finally, it is contradictory to the medicines regulations to manufacture and distribute Special Medication for a condition for which there is a licensed medication available that would appropriately meet a patient's needs.

5. Other considerations, wider ramifications and unintended consequences

5.1 Unlicensed as opposed to off-label use

While NICE's procedures envisage that comparators may be products which do not have a marketing authorisation for the indication defined in the Scope, we do not believe that, when this guidance was written, it was meant to encompass unlicensed use including compounding and a different route of administration. The DSU Report highlights that "it is the view of the MHRA that ocular use of bevacizumab constitutes an "unlicensed" as opposed to "off-label" use because of the manipulation of the licensed product." (p.8). Therefore bevacizumab for intravitreal use falls outside the definition of comparators under NICE's procedures.

5.2 Use of IVB does not represent best practice

The use of an unlicensed medicine cannot represent best practice for the treatment of RVO within the NHS and, in view of the availability of alternative licensed therapies, Novartis submits that any other conclusion would be very surprising. The intravitreal administration of a formulation which has undergone no regulatory scrutiny, in circumstances where the data supporting such use are very limited, cannot be viewed as "best practice", particularly in circumstances where alternative treatments, tested and authorised for such use, are available.

The General Medical Council ("GMC") prevailing guidance states that before prescribers use medicines outside their licence they must be satisfied: "that it would better serve the patient's needs than an appropriately licensed alternative" and "that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy".[16] The Royal Pharmaceutical Society provides similar advice to prescribing pharmacists and also requires pharmacists to dispense licensed, in preference to unlicensed, medicines where a suitable form is available.[17]

5.3 Other Considerations

Novartis also asserts that bevacizumab should not properly be considered as a comparator to ranibizumab in RVO for the following reasons:

- The use of an unlicensed comparator is inconsistent with the medicines licensing regimen and undermines the protection to public health provided by that regimen.

- On 22 December 2011, Novartis issued Judicial Review proceedings to seek a review of a decision by the Southampton, Hampshire, Isle of Wight, Portsmouth ("SHIP") Primary Care Trust Cluster to issue a policy recommending the use of bevacizumab to treat patients with wet AMD ("the Policy"). Novartis' position is that the fundamental flaw in the SHIP decision is that it undermined the licensing requirements for medicinal products, as set out in European Union law, by recommending a "switch" from ranibizumab, a licensed product, to bevacizumab, an unlicensed product, in circumstances where there is no unmet medical need.

  On 25 July 2012, the SHIP Cluster Board made a decision to revoke the Policy. At a further meeting of the SHIP Cluster Board on 24 September 2012, the Board made the following statement:

  "The Cluster Board formally confirms that the Policy decision concerning the use of bevacizumab for Wet Age Related Macular Degeneration, taken on 27 September 2011, has been revoked. There will be no policy relating to the commissioning of bevacizumab for wet AMD. The NICE TA155 (as updated in May 2012) is being followed by the SHIP PCT Cluster and, accordingly, funding for Lucentis is being made available in the SHIP PCT Cluster. The PCTs will not encourage the use of any other treatment for wet AMD."

- The recent decision of the European Court of Justice ("ECJ") in Case C-185/10 European Commission v Poland [2012] addressed the importation of unlicensed medicinal products, in circumstances where a licensed alternative was available.[7] The ECJ considered the circumstances in which unlicensed medicinal products could be placed on the market and stated:

  "It is apparent from the conditions set out in Article 5(1) of Directive 2011/83, read in the light of the fundamental objectives of that Directive, and, in particular the objective seeking to safeguard public health that the derogation provided for in that provision can only concern situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product be administered for which there is no authorised equivalent on the national market or which is unavailable on that market."

  The ECJ commented specifically in relation to the importation of unlicensed products on the grounds of costs:

  "Financial considerations cannot, in themselves, lead to recognition of the existence of such special needs capable of justifying the application of the derogation provided for in Article 5(1) of that Directive."

  In the context of the ECJ's judgment in relation to importation of unlicensed medicinal products, we believe it is equally clear that the derogation under Article 5(1) of Directive 2001/83/EC may not be relied upon for the manufacture and supply of unlicensed medicinal products on grounds of cost, where a licensed alternative is available. Accordingly, the manufacture of formulations of bevacizumab for the purposes of administration to NHS patients for the treatment of eye conditions is unlawful and reliance on a comparison with such unlicensed formulations for the purposes of NICE Guidance is inappropriate and improper.

- Any recommendation based on a comparison with an unlicensed product represents some endorsement by NICE of the unlicensed treatment, even if no explicit recommendation is made, as it implies that the use of an unlicensed product instead of licensed alternatives can be considered best practice. Taken in conjunction with the previous point, by accepting a comparison to bevacizumab as valid, NICE potentially exposes itself to liability in relation to its use.

- In circumstances where a licensed product is considered not to be cost effective in comparison with an unlicensed product and no other licensed treatment is available, this in effect constitutes a decision by NICE not to recommend treatment for a particular condition, as unlicensed treatments cannot be commissioned where there is a licensed alternative.

- The DSU Report contains some recognition of the unlicensed status of bevacizumab and its manufacture as a special. The production of "specials" is provided for as an exception under Article 5(1) of Directive 2001/83. Article 5(1) excludes from the Directive any medicinal product prescribed to fulfil an unmet special need, supplied in response to a bona fide unsolicited order and is formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his direct personal responsibility. There is no unmet special need for bevacizumab where ranibizumab is licensed for RVO. Industrial scale manufacture is not permitted – it is not permissible for pharmacists and manufacturers like Moorfields and Liverpool to manufacture, source, supply or stockpile large quantities of bevacizumab in advance of the need to supply it to a doctor who has prescribed it to a particular patient. The DSU Report does not assess whether the supply by Moorfields, Liverpool and other manufacturers is meeting the specials requirements set out above. Novartis' opinion is that such an assessment is required because, without it, NICE would appear to be indicating that all use can be considered whether or not that use is legitimate.

- Finally the delay in the approval of licensed VEGF inhibitors in RVO by NICE could result in an increase in the local compounding of bevacizumab within the NHS, which will put more patients at risk of infection and other complications.

6. Concluding statements

- In summary, there are quality concerns associated with IVB and the data supporting its efficacy, safety and use in RVO are very limited. There are also legal, regulatory and other considerations relating to IVB, which is an unlicensed medicine when it is reformulated for use in the eye. Novartis firmly believes it does not therefore provide a valid or proper comparator for ranibizumab and should not be considered in the guidance.

- NICE recommendations must be made on the evidence available at the time of appraisal, rather than delaying access to a licensed intervention in anticipation that further evidence may become available. Additionally, as highlighted by the appeal decision regarding the inclusion of rituximab as a comparator in lupus, the lack of data for an unlicensed comparator should not prevent access to a licensed intervention.

Appendix: Additional points of concern in the DSU Report

Page; paragraph	Statement	Novartis' response
8; 3	"The larger scale manufacturing units are more recent and carry out repackaging in bulk under tightly controlled conditions"	A medicine manufactured under a specials license may not be produced on an industrial scale. Therefore this statement is misleading.
24; 1	"Bevacizumab was also recommended *'to improve side effects and reduce the use of Lucentis'* in unspecified settings."	This statement is not linked to any specific indication or evidence. Furthermore, the European Commission state that cost grounds are not valid for the recommendation of one drug over another. Therefore this statement must be disregarded when appraising ranibizumab for the treatment of visual impairment due to MO secondary to RVO.
25; 3	"Ranibizumab is usually given once monthly"	Ranibizumab treatment is initiated on a monthly basis, but not necessarily for 6 months. It is given until maximum visual acuity is achieved.[6] Therefore the insinuation that ranibizumab would be associated with 6 injections over 6 months for all patients is not justified. Furthermore, in wAMD patients, the CATT trial reports that injections with bevacizumab are required more frequently than those with ranibizumab.[3]
27; 2	"The CATT study reports that in the first year, the mean number of injections received by those in the "on demand" treatment arm was 7"	7.7 injections of bevacizumab were given in CATT, not 7.[3, 18]
58; Figure 14	The CATT study is reported to have blinding of participants and personnel	The un-blinding due to patients knowing their billing fee, and resulting in over a third of patients at 2 years knowing what drug they were on, means that CATT does not have blinding of participants and personnel.[3]

76; 1	"Overall, adverse event rates were low in all bevacizumab and comparators groups"	Adverse event rates are not low in bevacizumab arms. For example in the CATT study, 39.3% of patients in the bevacizumab arm experiencing ≥1 serious adverse event should be considered very high, and is significantly greater that that seen with ranibizumab.
82; 1	"For example, this may occur when new technologies are used inconsistently across the NHS"	Avastin is not a new technology as it has been licensed since 2006 for intravenous use in cancer
117; Table A1	Derby City PCT are reported to use IVB	This use of IVB is due to the TANDEM trial being conducted in this PCT. This is therefore clinical trial use and cannot be considered as evidence to support routine use.

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