Section 21 Ophthalmological Preparations

Bevacizumab - Addition

Application submitted by International Council of Ophthalmology
1. Summary statement of the proposal for inclusion, change or deletion

We propose the inclusion of bevacizumab, an angiogenesis inhibitor that is used off label in the treatment of proliferative (neovascular) eye diseases. Although bevacizumab was initially approved by the US FDA for the treatment of colorectal cancer, the visual acuity and anatomical results that were observed when bevacizumab was used to treat age-related macular degeneration (AMD) led to widespread use of off-label bevacizumab for the treatment of exudative AMD by 2006. It was also observed that the adverse side effects associated with intravenous bevacizumab administration appeared to be avoided with intravitreal administration of the drug.

Since 2006, there have been reports of over fifty one ocular entities being treated with bevacizumab, generally those associated with neovascularization or vascular leakage as a consequence of an underlying disease. These include several types of choroidal neovascularization, retinal neovascularization, macular edema, neovascular glaucoma and radiation-induced eye diseases. Intravitreal bevacizumab administration is now used as a first line therapy for several diseases by many retina specialists and accounts for more than 50% of anti-VEGF administrations in the US. Additionally, the markedly lower cost of bevacizumab as compared to similarly effective drugs such as ranibizumab has led it its adoption for treatment of exudative AMD throughout the world. We therefore suggest that this drug be added to the WHO's existing list of essential eye medicines for use in developing countries.

2. Name of the focal point in WHO submitting or supporting the application (where relevant)

Ivo Kocur

3. Name of the organization(s) consulted and/or supporting the application

International Council of Ophthalmology

4. International Nonproprietary Name (INN, generic name) of the medicine

Bevacizumab

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

Bevacizumab 25 mg/ml

6. International availability - sources, if possible manufacturers and trade names

Bevacizumab is available in several places, including the US, Europe and India.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Individual medicine

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)
AMD is the leading cause of blindness in persons over 50 in developed countries. It is estimated that by 2020, as many as 7.5 million people worldwide over age 65 may have vision loss attributable to AMD. Ten to twenty percent of these persons are expected to have the neovascular form of the disease, and this form of the disease is responsible for 90% of all cases of severe vision loss due to AMD. If left untreated, this condition can lead to severe vision loss in low and middle income countries.

Bevacizumab is the predominant agent used to treat neovascular AMD worldwide. In addition, the intravitreal bevacizumab is increasingly being used as an adjunct treatment in other conditions that can result in choroidal and retinal neovascularization as well as in the management of macular edema. We therefore suggest that this drug be added to the WHO's existing list of essential eye medicines for use in developing countries.

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)

From a report prepared for the NHS's appraisal of bevacizumab:

"Various different doses of bevacizumab have been used in the published evidence sources, as well as different dose frequency schedules. The issue of optimal dose and frequency of bevacizumab has still not been conclusively resolved however this submission specifically relates to a standard dose of 1.25 mg of bevacizumab, and this is the dose most commonly used in published studies." The 1.25 mg dosage is administered monthly.

"Another consideration with bevacizumab is the preparation of doses for intravitreal injection. A common approach used in the clinical studies is for a pharmacy department to aseptically prepare a batch of syringes for use in a later clinic with one study reporting storage of such syringes for up to 14 days in a refrigerator. Each vial of Avastin® contains 100 mg of bevacizumab, sufficient for 80 doses however it would be difficult to extract this exact quantity. One method employed is to fill syringes with between 2.0 and 2.5 mg of bevacizumab (0.08 to 0.10 millilitre) resulting in up to 50 doses per vial of Avastin®."

"An alternative is for the clinical team to prepare doses in the treatment room immediately prior to administration using aseptic technique but this option may present greater risk of cross contamination. The number of doses extracted per vial could be reduced to a minimum of one, which will reduce the risk of cross contamination but will also eliminate some of the cost benefits presented by use of bevacizumab."

"Pre-packaged syringes of bevacizumab for intravitreal use are available to purchase from special manufacturing units. Moorfields Pharmaceuticals, of Moorfields NHS hospital, can supply syringes of 1.25 mg in 0.05 ml at £85 per syringe, excluding VAT and delivery charges. The syringes must be stored in a refrigerator and have an expiry date of six weeks from the date of manufacture, which would mean an effective expiry of about two to four weeks from receipt of delivery."

"Any compounding of a single vial of drug into multiple dose units will carry some risk of microbial and particulate cross contamination beyond that associated with preparation of a single dose. This risk can be minimised by performing the procedure in an aseptic clean room using trained staff and storing the finished product in a refrigerator."
10. Summary of comparative effectiveness in a variety of clinical settings:

In a recent report prepared for the NHS's appraisal of bevacizumab, the literature available on the effectiveness of bevacizumab for the treatment of AMD was summarized:

"There is a substantial volume of literature relating to the use of bevacizumab in neovascular AMD, the majority of it originating from reports of prospective case series’ or retrospective uncontrolled observational studies. A recently published systematic review of the literature included published data up to March 2008. Consequently an additional literature search was conducted and identified a further ten articles concerning the use of bevacizumab for neovascular AMD.

The additional are broadly in agreement with those studies included in the systematic review and therefore the review will constitute the principle source of evidence. The review included 23 studies of intravitreal and three of systemic (intravenous) administration of bevacizumab although meta-analyses are reported separately. Three of the included studies, all relating to intravitreal administration of bevacizumab, were randomised controlled studies (RCTs) that included at least one group treated with bevacizumab monotherapy. Studies were excluded that did not report results of visual acuity as the primary outcome and that included patients with indications other than neovascular AMD. The duration of studies ranged from four to 48 weeks with the majority between 12 and 24 weeks (mean 15). Most studies used an intravitreal bevacizumab dose of 1.25 mg. Results of visual acuity were converted to a single scale, the Early Treatment Diabetic Retinopathy Study score (ETDRS). A weighted mean result was calculated on this outcome and also the outcome measurement of central retinal thickness (CRT) with differences calculated between baseline and last reported result. Additionally, the quality of the included studies is subjectively assessed.

Regarding intravitreal administration, a total of 1,435 patients were included at baseline from all study populations (mean 61 per study, range 10 to 266). The three RCTs all showed that bevacizumab is more effective than photo-dynamic therapy although the quality of these studies was adjudged poor to reasonable. For study populations pertaining to intravitreal administration of bevacizumab only the weighted mean change in ETDRS score was 8.6 (range 2 to 26), and the weighted mean change (reduction) in central retinal thickness was 90 micrometres (range 46 to 190). The weighted mean change in visual acuity score was reduced to 8.0 when only studies that included doses < 2.0 mg of bevacizumab were included (n = 1,016). Although the studies differed in quality this did not have a large effect on the weighted outcome measures."

As per the review discussed in this appraisal, "The initial results of intravitreal bevacizumab treatment for exudative AMD led to acceptance of this therapy by clinicians around the world. Intravitreal bevacizumab accounts for more than 50% of all anti-VEGF therapy delivered for exudative AMD in the United States."

11. Summary of comparative evidence on safety*

In a recent report prepared for the NHS's appraisal of bevacizumab, the literature available on the safety of bevacizumab for the treatment of AMD was summarized:

"The principal source of evidence on the safety of bevacizumab for this appraisal is the systematic review published in 2009. Additionally some specific reports on the safety of intravitreal bevacizumab have been identified."
Table 1. Reported adverse events in 23 follow-up studies with intravitreal injections of bevacizumab for neovascular AMD in patients who received one or more injections (n = 1,396)

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of cases</th>
<th>Cumulative incidence per 100 patients</th>
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<tbody>
<tr>
<td>Posterior vitreous detachment</td>
<td>24</td>
<td>1.70</td>
</tr>
<tr>
<td>Pigment epithelial rupture</td>
<td>15</td>
<td>1.10</td>
</tr>
<tr>
<td>Vitritis or uveitis</td>
<td>8</td>
<td>0.56</td>
</tr>
<tr>
<td>Cataract progression</td>
<td>4</td>
<td>0.18</td>
</tr>
<tr>
<td>Subconjunctival haemorrhage</td>
<td>3</td>
<td>0.21</td>
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<tr>
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<td>Endophthalmitis</td>
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<td>0.14</td>
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<tr>
<td>Myocardial Infarction (MI)</td>
<td>2</td>
<td>0.14</td>
</tr>
<tr>
<td>MI death</td>
<td>1</td>
<td>0.07</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>1</td>
<td>0.07</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1</td>
<td>0.07</td>
</tr>
<tr>
<td>Blurred vision during first few days</td>
<td>Some reports, not quantified</td>
<td></td>
</tr>
</tbody>
</table>

The systematic review concluded that adverse events were rare amongst 1,400 patients who had received a total of several thousand intravitreal injections of bevacizumab. This result is supported by an internet surveillance programme of intravitreal bevacizumab in over 5,000 patients and more than 7,000 injections, and a 12 month follow-up study of nearly 1,200 patients and over 4,000 intravitreal injections. In the former report, with a mean follow-up of 3.5 months, the maximum incidence of any single event was 0.21% (table 3). In the latter report, that included a majority proportion of non-AMD patients, the total incidence of systemic adverse events was 1.5% (18 patients) and included hypertension, stroke, myocardial infarction, aneurysm, digit amputation, and fatalities, although none were conclusively and causally linked to bevacizumab.

The review authors state that the type and incidence of effects ‘does not seem to be very different from … two large RCTs of ranibizumab’. Numerous exclusion criteria were applied in the studies included in the review with the most common being cardiovascular and haematological criteria (e.g. hypertension, history of thromboembolic events, history of bleeding or coagulation abnormalities). This may bias the safety profile in favour of bevacizumab from results that might be obtained in practice unless similar criteria were applied.
As can be seen from the safety data, adverse events can be separated into different categories: those related to the intravitreal procedure itself, ocular effects of the drug, and systemic effects of the drug. The former would not be expected to differ from those experienced with ranibizumab as the method of administration is the same. A further complication when assessing safety in this population group is the underlying progressive disease state and any existing comorbidities in a predominantly elderly population. The conclusion of the safety data is only that the incidence of serious or severe adverse effects would appear to be small and that in general intravitreal bevacizumab appears to be well tolerated. The evidence so far available does not indicate undue risk of either local or systemic effects of bevacizumab.

12. Summary of available data on comparative cost** and cost-effectiveness within the pharmacological class or therapeutic group:

As per a recent report prepared for the NHS's appraisal of bevacizumab,⁴ using the assumption that a mean of ten doses of bevacizumab is obtained from each 100 mg vial of Avastin® table 3 shows that ranibizumab is 31 times more costly than bevacizumab per dose.
Table 3. Cost of therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Quantity per vial</th>
<th>Doses per vial</th>
<th>Cost per vial</th>
<th>Cost per dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>100 mg</td>
<td>10</td>
<td>£242.66</td>
<td>£24.27</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>3 mg</td>
<td>1</td>
<td>£761.20</td>
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</tbody>
</table>

In another, more extensive analysis comparing the cost effectiveness of bevacizumab and ranibizumab, the authors concluded that ranibizumab would have to be at least 2.5 times more efficacious than bevacizumab (or bevacizumab would have to be only 40% as effective as ranibizumab) for ranibizumab to be considered cost-effective at an incremental threshold of about £30,000 per quality adjusted life year. The authors concluded that the price of ranibizumab would have to be drastically reduced for it to be cost effective.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Although Bevacizumab is not approved by the FDA for the treatment of retinal diseases, it is used off label for the treatment of these diseases in the US and elsewhere.


Bevacizumab meets United States, British and European pharmacopoeial standards.

15. Proposed (new/adapted) text for the WHO Model Formulary

Per http://dailymed.nlm.nih.gov as well as other sources:

**How supplied**

AVASTIN is supplied as 4 mL and 16 mL of a sterile solution in single-use glass vials to deliver 100 and 400 mg of Bevacizumab per vial, respectively.

**Dosing**

1.25 mg of bevacizumab once monthly

**Contraindications**

None.

**Precautions (Note: the list of precautions is available for intravenous injections, not for intravitreal injections)**

**Gastrointestinal Perforations**

Serious and sometimes fatal gastrointestinal perforation occurs at a higher incidence in Avastin treated patients compared to controls. The incidence of gastrointestinal perforation ranged from 0.3 to 2.4% across clinical studies.
The typical presentation may include abdominal pain, nausea, emesis, constipation, and fever. Perforation can be complicated by intra-abdominal abscess and fistula formation. The majority of cases occurred within the first 50 days of initiation of Avastin.

Discontinue Avastin in patients with gastrointestinal perforation.

**Surgery and Wound Healing Complications**

Avastin impairs wound healing in animal models. In clinical trials, administration of Avastin was not allowed until at least 28 days after surgery. In a controlled clinical trial, the incidence of wound healing complications, including serious and fatal complications, in patients with mCRC who underwent surgery during the course of Avastin treatment was 15% and in patients who did not receive Avastin, was 4%.

Avastin should not be initiated for at least 28 days following surgery and until the surgical wound is fully healed. Discontinue Avastin in patients with wound healing complications requiring medical intervention.

The appropriate interval between the last dose of Avastin and elective surgery is unknown; however, the half-life of Avastin is estimated to be 20 days. Suspend Avastin for at least 28 days prior to elective surgery. Do not administer Avastin until the wound is fully healed.

**Hemorrhage**

Avastin can result in two distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin compared to patients receiving only chemotherapy. Across indications, the incidence of Grade ≥ 3 hemorrhagic events among patients receiving Avastin ranged from 1.2 to 4.6%.

Serious or fatal pulmonary hemorrhage occurred in four of 13 (31%) patients with squamous cell histology and two of 53 (4%) patients with non-squamous non-small cell lung cancer receiving Avastin and chemotherapy compared to none of the 32 (0%) patients receiving chemotherapy alone.

In clinical studies in non–small cell lung cancer where patients with CNS metastases who completed radiation and surgery more than 4 weeks prior to the start of Avastin were evaluated with serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of 83 Avastin-treated patients (rate 1.2%, 95% CI 0.06%–5.93%).

Intracranial hemorrhage occurred in 8 of 163 patients with previously treated glioblastoma; two patients had Grade 3–4 hemorrhage.

Do not administer Avastin to patients with recent history of hemoptysis of ≥ 1/2 teaspoon of red blood. Discontinue Avastin in patients with hemorrhage.
Non-Gastrointestinal Fistula Formation

Serious and sometimes fatal non-gastrointestinal fistula formation involving tracheo-esophageal, bronchopleural, biliary, vaginal, renal and bladder sites occurs at a higher incidence in Avastin-treated patients compared to controls. The incidence of non-gastrointestinal perforation was ≤ 0.3% in clinical studies. Most events occurred within the first 6 months of Avastin therapy.

Discontinue Avastin in patients with fistula formation involving an internal organ.

Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a higher incidence in patients receiving Avastin compared to those in the control arm. Across indications, the incidence of Grade ≥ 3 ATE in the Avastin containing arms was 2.6% compared to 0.8% in the control arms. Among patients receiving Avastin in combination with chemotherapy, the risk of developing ATE during therapy was increased in patients with a history of arterial thromboembolism, or age greater than 65 years.

The safety of resumption of Avastin therapy after resolution of an ATE has not been studied. Discontinue Avastin in patients who experience a severe ATE.

Hypertension

The incidence of severe hypertension is increased in patients receiving Avastin as compared to controls. Across clinical studies the incidence of Grade 3 or 4 hypertension ranged from 5-18%.

Monitor blood pressure every two to three weeks during treatment with Avastin. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor blood pressure at regular intervals in patients with Avastin-induced or -exacerbated hypertension after discontinuation of Avastin.

Temporarily suspend Avastin in patients with severe hypertension that is not controlled with medical management. Discontinue Avastin in patients with hypertensive crisis or hypertensive encephalopathy.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

RPLS has been reported with an incidence of < 0.1% in clinical studies. The onset of symptoms occurred from 16 hours to 1 year after initiation of Avastin. RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging (MRI) is necessary to confirm the diagnosis of RPLS.

Discontinue Avastin in patients developing RPLS. Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating Avastin therapy in patients previously experiencing RPLS is not known.
Proteinuria
The incidence and severity of proteinuria is increased in patients receiving Avastin as compared to controls. Nephrotic syndrome occurred in < 1% of patients receiving Avastin in clinical trials, in some instances with fatal outcome. In a published case series, kidney biopsy of six patients with proteinuria showed findings consistent with thrombotic microangiopathy.

Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during Avastin therapy. Patients with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection.

Suspend Avastin administration for ≥ 2 grams of proteinuria/24 hours and resume when proteinuria is < 2 gm/24 hours. Discontinue Avastin in patients with nephrotic syndrome. Data from a postmarketing safety study showed poor correlation between UPCR (Urine Protein/Creatinine Ratio) and 24 hour urine protein (Pearson Correlation 0.39 (95% CI 0.17, 0.57). The safety of continued Avastin treatment in patients with moderate to severe proteinuria has not been evaluated.

Infusion Reactions
Infusion reactions reported in the clinical trials and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis.

In clinical studies, infusion reactions with the first dose of Avastin were uncommon (< 3%) and severe reactions occurred in 0.2% of patients.

Stop infusion if a severe infusion reaction occurs and administer appropriate medical therapy.

Ovarian Failure
The incidence of ovarian failure was higher (34% vs. 2%) in premenopausal women receiving Avastin in combination with mFOLFOX chemotherapy as compared to those receiving mFOLFOX chemotherapy alone for adjuvant treatment for colorectal cancer, a use for which Avastin is not approved. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin.

Drug interactions
A drug interaction study was performed in which irinotecan was administered as part of the FOLFIRI regimen with or without Avastin. The results demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan or its active metabolite SN38.

In a randomized study in 99 patients with NSCLC, based on limited data, there did not appear to be a difference in the mean exposure of either carboplatin or paclitaxel when each was administered alone or in combination with Avastin. However, 3 of the 8 patients receiving Avastin plus paclitaxel/carboplatin had substantially lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel/carboplatin without Avastin had a greater paclitaxel exposure at Day 63 than at Day 0.
In another study, there was no difference in the mean exposure of interferon alfa administered in combination with Avastin when compared to interferon alfa alone.

**Pregnancy use**

Based on animal data, may cause fetal harm

**Adverse effects**

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