(1) Does the application adequately address the issue of the public health need for the medicine?

Yes ☐ No ☒

Please provide brief details:

Macular degeneration (MD) is a common cause of acquired blindness across the world. It leads to significant loss of health life years and this effect is higher in less developed regions of the world [1]. The burden is possibly higher because of easy availability of treatments.

There is a public health concern that stems from the current inclusion of bevacizumab (Avastin®) for treatment of wet-macular degeneration (WMD) through intravitreal (IVB) injection. This is not a manufacturer or health regulatory body approved indication for the available formulation of this drug. The off-label usage has caused multiple cases of endophthalmitis in reports from Egypt, Iran and India. These are clustered cases likely related to inappropriate handling of the single-use medication vials which are not designed for multiple uses during administration or compounding. The overall incidence of endophthalmitis among IVB injection of Avastin® remains low.

(2) Alternatives to bevacizumab

For treatment of WMD in adults, 2 other medications have been recommended in the application. Ranibizumab (Lucentis®) and aflibercept (Eylea®) are internationally approved for this and other ophthalmologic indications. A fourth medication, Macugen® is also available but is an older and less frequently used drug. These medications are highly efficacious in the treatment of WMD. All anti-VEGF IVB treatments are given on a monthly (except every 8 weeks for Eylea®) basis for at least 3-4 months to a year and then continued on an as-needed (PRN) basis.

Several trials have compared the anti-VEGF drugs, primarily Lucentis® against Avastin® and found little to no significant difference in safety or efficacy. [3-8]

Prior to the introduction of anti-VEGF medications, treatment of progressive diabetic retinopathy and WMD were done by laser photocoagulation. Another approach is through photodynamic therapy (PDT) with Visudyne™. Laser treatment has its limitations, however, as only 10-15%
of lesions are amenable to therapy and there is a 50% chance of recurrent vascular leakage in 2 years. [9]

Of note, Lucentis® and Avantis® are both manufactured by Genentech (Roche) who have also brought forward this application. As it stands, Genentech have a strong financial incentive for Avantis® to be removed from the EML for ophthalmologic indications.

(3) **Toxicities related to bevacizumab and its alternative agents**

Bevacizumab is an agent that was developed for intravenous use as an anticancer drug. There has been a concern that intravitreal injection of this drug leads to higher systemic absorption and effects compared to ranibizumab. This has been shown primarily in the CATT study and the effect is very small. [3] A large meta-analysis done by the Cochrane group on non-industry sponsored trials found no significant difference in systemic adverse effects between Avastin® and Lucentis® except for gastrointestinal disturbances. [10]

The major adverse effect related to off-label use of Avastin® is related to its redistribution from the 100mg vial into smaller injections for intravitreal use. These introduce a higher risk of contamination and subsequent endophthalmitis. However, when handled correctly under sterile conditions, this is a rare complication. Results from the comparison of age-related macular degeneration treatments trial (CATT) post-injection endophthalmitis to have an incidence of 1 in 1700 patients (0.06%). [11]

**ADDITIONAL CONSIDERATIONS:**

(1) **Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?**

- Yes [x]  
- No [ ]

Please provide brief details:

Trained ophthalmologists only will be able to administer the medication intravitreally. The procedure typically occurs in the sterile setting of an operating room. However, the issue is that drawing multiple doses from a single vial has a high risk of contamination, regardless of operator. This risk is increased exponentially when there are breaches in sterile technique, which can lead to vision-threatening endophthalmitis.

High quality training and facilities are required for pharmaceutical compounding of this medication. According the United States Pharmacopeia (USP), the preparation of intravitreal Avastin® into aliquots may be categorised as medium-risk level for sterile compounding. It is recommended
that all compounding be done at a laminar airflow workbench, under a hood with routine disinfection and air quality control per ISO class 5 standards.

(2) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes ☐ No ☐

Please provide brief details:

The use of bevacizumab intravitreally is an off-label use of this medication. This is, however, a widely-accepted use by ophthalmologists who have used it intravitreally for years.

(3) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes ☐ No ☒

Please provide brief details:

(4) Please comment briefly on issues regarding cost and affordability of this medicine.

Use of Avastin® for intravitreal injection is much more affordable than chemotherapy because of the smaller dose required. In contrast, the cost of Lucenta® and Eylea® is much higher. The overall costs of therapy vary widely ($400-2000/dose) however use of Lucenta® and Eylea® is consistently more expensive than Avastin® which is available for $55 or less.

Treatment with simple laser photocoagulation tends to be cheaper than anti-VEGF therapy, however, the efficacy is also lower. The cost of laser therapy also greatly varies ($150-2600) and is dependent on the degree of neovascularisation that needs to be treated. PDT may also be an expensive option depending on the availability of Visudyne™ and can cost anywhere between $600-1800 per treatment.

Previously, Italian authorities have brought suit against Roche and Novartis for colluding over the prices of Lucentis® and were forced to decrease the sales price. [2] NICE, in the UK has also acted against these companies to push for approval of Avastin® for ophthalmologic indications against resistance by Novartis. [12]

(5) Any additional comments?

Use of bevacizumab (Avastin®) intravitreally is an off-label use and associated with a significant risk of infection that may lead to blindness via endophthalmitis. Beyond manufacturing changes, practitioners and
compounders can take extra care while repurposing the medication from a single vial into multiple syringes to minimise risk of contamination. For patients who have no other treatment options, the risk-vs-benefit of off-label bevacizumab therapy must be made clear and alternative treatments with laser therapy should be discussed.

An additional concern with compounded bevacizumab is variability in protein concentrations, however, the clinical significance of this variation is not clear. [13]

Another potential concern with bevacizumab is availability of counterfeit drugs. There have been previous reports of counterfeit Avastin® in markets in China, the US and Iran. It is possible that removal from the EML and national formularies, prescribers may turn to less reliable sources such as these to continue treatment for their patients.

(6) Please frame the decisions and recommendations that the Expert Committee could make.

Off-label use of Avastin® for this indication provides an affordable treatment option for patients with DMO and WMD, however, this comes at a substantial risk for infection due to its usage for an indication it is not designed for. Although, if no affordable therapy is available for patients, they are likely to have progressive vision loss due to their disease regardless.

Best practice compounding with aseptic technique is absolutely essential in order to avoid the risk of post-injection infections. WHO should recommend strict guidelines for preparation of Avastin® for intravitreal use so that treatment for macular degeneration can remain affordable for the majority of patients in lower and middle-income countries.

(7) References (if required)


