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

Yes  $\times$

Age-related macular degeneration (AMD or ARMD), is a medical condition that usually affects older adults and results in a loss of vision in the center of the visual field (the macula) because of damage to the retina. It occurs in "dry" and "wet" forms. It is a major cause of blindness and visual impairment in older adults (>50 years). It is affecting 30-50 million people worldwide. As a result of the increased life expectancy and growth of the elderly population, the cases of AMD are expected to increase by at least 50% by the year 2020.

The prevalence rate of clinical significant Diabetic macular edema (DME) is approximately 6-10%, with visual impairment due to DME affecting a small proportion (approximately 1-3%) of the diabetic population.

Retinal vein occlusion (RVO), either branch RVO (BRVO) or central RVO (CRVO), is the second most frequent retinal disorder after diabetic retinopathy.

Approximately 16.4 million adults are affected worldwide, with 13.9 million having BRVO and 2.5 million having CRVO. The annual incidences of BRVO and CRVO are 0.12% and 0.03-0.04%, respectively.

Pathological myopia (PM) is a leading cause of vision loss, especially in a younger population (<50 years of age). Prevalence rates of PM vary between 2 and 9%, depending on the race and age of the population. The most vision threatening complication in patients with PM is Choroidal neovascularization (CNV).

New drugs, the anti-VEGF, are available for these pathologies but they have also raised concerns over the economic impact of medical innovation.

(2) Have all important studies that you are aware of been included in the application?

Yes  $\times$

At the time of submission all important studies were included but several studies are ongoing.


(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

Yes X

Ranibizumab (Lucentis®) an anti-VEGF (vascular endothelial growth factor) is indicated in adults for:

- the treatment of neovascular (wet) age-related macular degeneration (AMD);
- the treatment of visual impairment due to diabetic macular edema (DME);
- the treatment of visual impairment due to macular edema secondary to retinal-vein occlusion (branch RVO or central RVO);
- the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM).

There are numerous studies documenting the efficacy of Ranibizumab in the above indications.

The actual benefit of Ranibizumab 10 mg/ml is substantial in the treatment of patients with 1) exsudative age-related macular degeneration (AMD) with subfoveal choroidal neovascularisation; 2) visual impairment of 5/10 or less as a result of diabetic macular edema in diffuse forms of the disease or with leaks close to the center of the macula in whom diabetic care has been optimized ; 3) visual impairment due to macular edema secondary to branch or central RVO and 4) visual impairment due to choroidal neovascularisation secondary to pathologic myopia.

However it is too early to assess its true position in large settings and real life prescribing worldwide.

Other products are being tested and off-label bevacizumab is more cost effective.

(4) Is there evidence of efficacy in diverse settings and/or populations?

Yes X

Thorough patient assessment is essential for the proper use of Ranibizumab since the target population is well defined in the marketing authorizations.
Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes  

The serious adverse events related to the injection procedure included endophthalmitis, rhegmatogenous retinal detachment, retinal tears and iatrogenic traumatic cataracts as well as intraocular inflammation and increased intraocular pressure.

Women of child-bearing potential should use effective contraception during treatment. Ranibizumab should not be used during pregnancy unless the expected benefit outweighs the potential risk to the foetus. For women who wish to become pregnant and who have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child.

The safety issue is still controversial and good pharmacovigilance is necessary. [De Rosa M, Messori A The safety of bevacizumab and ranibizumab in clinical studies. Int Ophthamol. 2015 Feb 3. Epub ahead of print]

ADDITIONAL CONSIDERATIONS:

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

Yes  

Ranibizumab (Lucentis®) is available as single-use vial for intravitreal use only. It must be prescribed and administered by a qualified ophthalmologist experienced in intravitreal injections.

Experience with this treatment is limited in groups other than Caucasians.

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

Yes  

The FDA approved ranibizumab (Lucentis®) to treat diabetic retinopathy (DR) in patients with diabetic macular edema (DME). The FDA reviewed this new use for the drug under the agency’s priority review program, which provides for an expedited review of drugs that demonstrate the potential to be a significant improvement in safety or effectiveness in the treatment of a serious condition. The FDA previously had approved ranibizumab to treat DME (in 2012) and macular edema secondary to retinal vein occlusions, both of which cause fluid to leak into the macula, which can result in blurred vision.
Ranibizumab is also approved in the United States for the treatment of neovascular (wet) age-related macular degeneration.

Ranibizumab is administered by intravitreal injection once monthly.

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

No  X

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

Other products are being tested and off-label bevacizumab [L01XC07 (used primarily in colo-rectal cancers)] is more cost effective. Dr. Joshua D. Stein from University of Michigan in Ann Arbor: "The main message of our study is to highlight for clinicians and policy makers that bevacizumab is a considerably more cost effective treatment option than ranibizumab for treatment of neovascular AMD and that incentivizing providers to treat their patients with bevacizumab may lead to considerable cost savings with minimal impact on patient outcomes," [Bevacizumab Beats Ranibizumab in Cost-Effectiveness Study for Macular Degeneration. Medscape. Feb 13, 2014.]

(10) Any additional comments?

It should be noted that Aflibercept [(Eylea®) S01LA05] is indicated for the treatment of patients with: Neovascular (Wet) Age-Related Macular Degeneration (AMD) and Macular Edema Following Central Retinal Vein Occlusion (CRVO). Aflibercept (Eylea®) does not provide any improvement in actual benefit compared with ranibizumab (Lucentis®) for adults in the treatment of 1) exudative retro-foveal AMD and 2) visual impairment due to macular edema secondary to central retinal vein occlusion (CRVO).


Pegaptanib [(Macugen®) S01LA05] has become obsolete.
I will recommend the addition of RANIBIZUMAB vials 10mg/ml to the EML for:

1) exudative age-related macular degeneration (AMD) with subfoveal choroidal neovascularisation;
2) visual impairment of 5/10 or less as a result of diabetic macular edema in diffuse forms of the disease or with leaks close to the center of the macula in whom diabetic care has been optimized;
3) visual impairment due to macular edema secondary to branch or central RVO; 4) visual impairment due to choroidal neovascularisation secondary to pathologic myopia.

The target population should be well identified for the prescription conditions. Good pharmacovigilance is necessary for all the anti-VEGF.