

December 18, 2019

Harold Paz, MD  
Chief Medical Officer  
Aetna  
151 Farmington Avenue  
Hartford, CT 06156

Dear Dr. Paz,

The American Society of Retina Specialists writes to request a teleconference to discuss Aetna's Vascular Endothelial Growth Factor (VEGF) Inhibitors for Ocular Indications [Medicare] effective January 1, 2020. We oppose this fail-first approach because it requires that bevacizumab (Avastin), an off-label, repackaged drug, which has not received FDA approval for intravitreal injections, be used unsuccessfully before the use of one of the Food and Drug Administration (FDA)-approved drugs, aflibercept (Eylea) and ranibizumab (Lucentis). Making a patient fail a therapy such as Avastin subjects them to increased risk of vision loss before a more effective therapy can be started. While lower-cost Avastin can be effective for some patients and many retina specialists start with Avastin, we believe its use should not be required. This policy also prevents physicians from providing appropriate care to meet patients' unique medical needs.

ASRS is the largest retina organization in the world, representing over 3,500 board certified ophthalmologists who have completed fellowship training in the medical and surgical treatment of retinal diseases. The mission of the ASRS is to provide a collegial open forum for education, to advance the understanding and treatment of vitreoretinal diseases, and to enhance the ability of its members to provide the highest quality of patient care.

Avastin, Eylea and Lucentis are not interchangeable and their efficacy, safety and clinical usage must be considered when determining the most appropriate drug for a specific disease presentation given individual patient's co-morbidities and risk. Ultimately, the retina specialist utilizes clinical judgment to select the best drug to use for treatment. This ability to individualize treatment and select the most efficacious agent for each patient is key to the major improvements we have gained in recovering and maintaining visual acuity and retinal function in our patients with blinding diseases of the retina. The studies below highlight their differences.

#### **Diabetic Macular Edema: Protocol T Trial**

The randomized Diabetic Retinopathy Clinical Research Network (DRCRnet) Protocol T study, funded by the National Eye Institute, compared Eylea, Lucentis and Avastin. The Protocol T Year Two study found a greater need for photocoagulation treatment for the Avastin group and Avastin had an inferior effect on reducing retinal fluid, as measured by Optical Coherence Therapy (OCT), when compared to Lucentis and Eylea.<sup>i,iii</sup>

This is particularly concerning, because of what we know based on previous trials including RISE/RIDE<sup>iii</sup> and VISTA/VIVID<sup>iv</sup>. Patients in these trials that received delayed treatment never caught up to their counterparts that received treatment at the onset due to the effects of chronic macular edema. The concern with application of a fail-first approach is that a similar delay would transpire in patients receiving care for diabetic macular edema, leading to a poorer final visual prognosis.

### **Neovascular Age-Related Macular Degeneration: The CATT Study**

The Comparison of Age Related Macular Degeneration Treatment Trials (CATT study year 1 and CATT study year 2) clinical effectiveness study, sponsored by the National Institute of Health, compared 0.5 mg Lucentis to off-label Avastin for the treatment of wet AMD employing both a monthly and pro re nata (prn) treatment regimen. While the overall visual and safety outcomes reported in the CATT study were similar between Avastin and Lucentis treatment, Lucentis demonstrated greater anatomic improvements on OCT as compared to off-label Avastin.<sup>v</sup> Although this study did not evaluate Eylea, the VIEW studies compared Eylea to Lucentis, and found Eylea to be superior to Lucentis in inducing complete resolution of retinal edema and likely better than Avastin when the data from both studies are combined.<sup>vi</sup>

There is extensive patient-to-patient variation in the responsiveness of edema to anti-VEGF therapy, with some patients requiring at least monthly injections to dry the retina, and others requiring only a few within a year. Given this variability, physicians should have the ability to tailor the treatment to the individual patient and the patient's response to therapy. To restrict access to the most powerful drying agent will inhibit our ability to fully treat the disease activity in the most severe cases. Persistent edema has been correlated with poorer visual outcomes in a variety of studies, including a post hoc analysis of the VIEW studies looking at patients with persistent retinal fluid following the initial 3 monthly anti-VEGF injections. These patients with persistent fluid were less common following Eylea treatment than Lucentis treatment, and in this population, the visual acuity gain from baseline to week 52 was greater with monthly Eylea compared with monthly Lucentis ( $p < 0.01$ ). The analysis suggests that a more difficult to treat, persistent fluid, wet AMD patient population, may benefit more from monthly Eylea compared to monthly Lucentis.<sup>vii</sup>

### **Safety**

Several studies report that systemic exposure of Avastin after intravitreal injection is up to 70 times higher than that of Lucentis, and caution is recommended for its use in at-risk populations. For chronic diseases such as AMD, requiring intravitreal Avastin injections in patients who have experienced a recent stroke or heart attack could potentially increase the risk of systemic complications and the risk of liability to Aetna.<sup>viii,ix</sup>

An additional study found that large doses of anti-VEGF agents used in cancer treatment carry an increased risk of thromboembolic events and there are only limited data about the safety of smaller doses in patients who have experienced a recent stroke or heart attack, as these patients were excluded from the registration trials.<sup>x</sup> The increased systemic anti-VEGF exposure with intravitreal Avastin compared to Lucentis is concerning in patients at high risk of additional thromboembolic events.

While the FDA has improved its oversight of outsourcing facilities, periodic recalls continue to occur. In some cases, the recall is related to the sterility of the drug, but more often, it is related to the container (i.e., syringe). For example, AmEx Pharmacy recently voluntarily recalled one lot of Avastin due to ocular damage that may occur due to difficulties expressing Avastin with the Monoject syringe. In the past two years, there have been class action lawsuits directed against doctors who use and pharmacies that repackage Avastin because of silicone droplets present in the syringes used for Avastin. Therefore, this

step policy may subject Aetna to increased litigation if the insurance company is dictating therapy, rather than allowing the patient and the physician to make the decision.

**Access**

Numerous factors have increased the costs of repackaging including that outsourcing facilities must comply with the Current Good Manufacturing Practices requirements, including USP <789> testing requirements. As a result, there continue to be shortages of Avastin as some facilities have failed to meet these requirements or shut down, leaving their Avastin business behind. Consequently, the remaining outsourcing facilities such as Avella, have had recent delays in filling orders for Avastin, as they try to meet increasing demand.

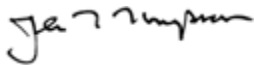
Finally, we do not believe that it is in the best interest of patients to issue new step therapy guidance in the middle of open enrollment season, when some have selected plans without knowledge of the new limitations imposed by Aetna. Patients do not have enough time to consider these changes and discuss them with their providers. The consequence of choosing a plan that has a one-size-fits all policy such as step therapy, could be detrimental to the vision of patients with unique treatment needs.

In summary, we strongly urge Aetna to reverse its fail-first policy and allow retina specialists and their patients to make judicious choices based on the patient's unique risk factors, clinical appearance, availability of compounded drugs, and economic requirements. We look forward to a response from you. Please do not hesitate to contact ASRS Director of Practice Management, Monica Horton, [monica.horton@asrs.org](mailto:monica.horton@asrs.org), if you have questions or would like to coordinate a meeting. Thank you for your consideration.

Sincerely,



Robert Avery, MD  
ASRS Chair, Practice Management Committee



John Thompson, MD  
ASRS Practice Management Committee Member



Ankoor Shah, MD  
ASRS Practice Management Committee Member

CC: Robert McDonough, Head of Clinical Policy Research & Development  
David Epstein, Aetna, Medical Director

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<sup>i</sup> The New England Journal of Medicine, The Diabetic Retinopathy Clinical Research Network, “Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema,” (also known as Protocol T, Year 1), March 26, 2015. <http://www.nejm.org/doi/full/10.1056/NEJMoa1414264#t=article>

<sup>ii</sup> Wells JA, Glassman AR, Ayala AR, et al; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial [published online February 27, 2016]. *Ophthalmol.* 2016;123(6):1351-1359.

<sup>iii</sup> Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, Gibson A, Sy J, Rundle AC, Hopkins JJ, Rubio RG, Ehrlich JS; **RISE and RIDE Research Group**. *Ophthalmology*. 2012 Apr;119(4):789-801. doi: 10.1016/j.ophtha.2011.12.039. Epub 2012 Feb 11.

<sup>iv</sup> Heier JS, Korobelnik JF, Brown DM, et al. Intravitreal aflibercept for diabetic macular edema: 148-week results from the VISTA and VIVID Studies [published online September 17, 2016]. *Ophthalmology* 2016;123(11):2376-2385. doi:10.1016/j.ophtha.2016.07.032.

<sup>v</sup> Comparison of Age-Related Macular Degeneration Treatment Trials (CATT) Research Group, Martin DF, Maguire, MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, Toth C, Redford M, Ferris FL 3rd. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012 Jul;119(7):1388-98.

<sup>vi</sup> Schmidt-Erfurth U, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology*. 2014 Jan; 121(1):193-201.

<sup>vii</sup> Jaffe GJ, Kaiser PK, Thompson D, et al. Differential Response to Anti-VEGF Regimens in Age-Related Macular Degeneration Patients with Early Persistent Retinal Fluid. *Ophthalmology*, 2016; 123(9): 1856 – 1864.

<sup>viii</sup> Hanhart, J., Comaneshter, D.S., Freier-Dror, Y. et al. Mortality associated with bevacizumab intravitreal injections in age-related macular degeneration patients after acute myocardial infarct: a retrospective population-based survival analysis. *Graefes Arch Clin Exp Ophthalmol* (2018) 256: 651. <https://doi.org/10.1007/s00417-018-3917-9>

<sup>ix</sup> Hanhart J., Comaneshner, DS, Vinker S., Mortality after a cerebrovascular event in age-related macular degeneration patients treated with bevacizumab ocular injections. *ACTA Ophthalmological* (2018) <https://doi.org/10.1111/aos.13731>

<sup>x</sup> Avery RL, et al. What is the evidence for systemic effects of intravitreal anti-VEGF agents, and should we be concerned? *Br J Ophthalmol*. 2014 Jun;98 Suppl 1:i7-i10.