UNITED STATES INTERNATIONAL TRADE COMMISSION
WASHINGTON, D.C.

BEFORE THE HONORABLE CLARK S. CHENEY
ADMINISTRATIVE LAW JUDGE

In the Matter of CERTAIN PRE-FILLED SYRINGES FOR INTRAVITREAL INJECTION AND COMPONENTS THEREOF	Inv. No. 337-TA-1207

OPENING EXPERT REPORT OF SZILÁRD KISS, M.D.

these patients from experiencing permanent blindness, and irreversible vision loss in other patients, the ITC should not exclude EYLEA PFS, or else exempt existing patients from the remedy and delay its effective date as long as possible.

VII. OTHER TREATMENTS, IF AVAILABLE, ARE LESS EFFECTIVE, INFERIOR, AND IN SOME CASES, UNSAFE

A. LUCENTIS Is Less Effective Than and Inferior to EYLEA PFS

47. Assuming an exclusion order is granted against EYLEA PFS and LUCENTIS is available in enough supply as an anti-VEGF treatment option, I believe LUCENTIS is less effective than, and inferior to, EYLEA PFS.[39]

48. First, the EYLEA and LUCENTIS molecules are not the same. Given its structure as a recombinant fusion protein, EYLEA is more likely to bind VEGF targets more tightly than LUCENTIS, which is an antibody fragment, and not able to deliver as strong of a VEGF inhibition.[40] The EYLEA molecule is also much larger than LUCENTIS, so it does not clear out of the eye as quickly.[41] EYLEA also binds the placental growth factor, another useful secondary molecule that can help treat wAMD and DR, which LUCENTIS does not do.[42]

49. LUCENTIS is also less effective than EYLEA for certain indications. *See, e.g.,* REGITC00376350; REGITC00377221. For example, although EYLEA and LUCENTIS are both anti-VEGF treatments, LUCENTIS has been shown to be significantly less effective in

[39] The 2019 Preferences and Trends (PAT) Membership Survey, conducted by the American Society of Retinal Specialists, also showed nearly 80 percent of retinal specialists would use EYLEA to treat new-onset wet AMD, if AVASTIN, LUCENTIS and EYLEA cost the same. *See*, Stone TW, Hahn P, eds. ASRS 2019 Preferences and Trends Membership Survey. Chicago, IL. American Society of Retina Specialists; 2019 at slide 5.
[40] Tschulakow A, Christner S, Julien S, Ludinsky M, van der Giet M, Schraermeyer U. Effects of a single intravitreal injection of aflibercept and ranibizumab on glomeruli of monkeys. PLoS One. 2014;9(11):e113701. Published 2014 Nov 21. doi:10.1371/journal.pone.0113701
[41] Raj Sharma, Yog; Tripathy, Koushik; Venkatesh, Pradeep; Gogia, Varun (2015): Aflibercept – How does it compare with other Anti-VEGF Drugs?. figshare. Journal contribution. https://doi.org/10.6084/m9.figshare.1373843.v2
[42] Nguyen QD, De Falco S, Behar-Cohen F, Lam WC, Li X, Reichhart N, Ricci F, Pluim J, Li WW. Placental growth factor and its potential role in diabetic retinopathy and other ocular neovascular diseases. Acta Ophthalmol. 2018 Feb;96(1):e1-e9. doi: 10.1111/aos.13325. Epub 2016 Nov 22. PMID: 27874278; PMCID: PMC5811779.

improving vision in diabetic patients with the worst vision due to swelling of the retina.[43,44] Diabetic patients make up a large portion of my practice, and I only use ELYEA PFS for these patients. If forced to switch to LUCENTIS PFS, the visual outcomes in these patients would suffer, even if LUCENTIS was administered as recommended. The difference in effectiveness can mean the difference in being able to obtain a driver's license and functioning at work.

50. LUCENTIS is inferior to EYLEA for the additional reason that it must be dosed more frequently. Indeed, EYLEA is recommended for intravitreal injection once a month for the first three months for wAMD, once a month for the first five months for DME and DR, and can thereafter be injected every two months for wAMD, DME and DR.[45] *See* REGITC00143489. LUCENTIS, by contrast, must be injected monthly for all its approved indications. *See* NOVITC(CH)00165856. Regeneron clinical studies showed that EYLEA administered every two months was clinically equivalent to LUCENTIS dosed monthly.[46,47] Given the burden and risk associated with intravitreal injections, virtually any retinal specialist would agree that fewer injections into the eye is preferred whenever possible. [redacted]

[43] Wells et al., Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema, N Engl J Med, 2015 Mar. 26;372(13):1193-203, https://www.nejm.org/doi/full/10.1056/NEJMoa1414264.
[44] Steinle, Nathan C. "Lessons from DRCR.net Protocol T." *Retina Specialist*, 5 Mar. 2015, www.retina-specialist.com/article/lessons-from-drcrnet-protocol-t.
[45] MEfRVO is recommended to be dosed monthly.
[46] Raj Sharma, Yog; Tripathy, Koushik; Venkatesh, Pradeep; Gogia, Varun (2015): Aflibercept – How does it compare with other Anti-VEGF Drugs?. figshare. Journal contribution. https://doi.org/10.6084/m9.figshare.1373843.v2
[47] A March 2020 publication I authored found that in the 2014-2016 time period, some physicians were underdosing patients and as a result there was no difference in dosing frequencies between EYLEA and LUCENTIS in those patients. NOVITC(US)00388317. The paper found that the underdosing was a cause for concern that may result in suboptimal vision outcomes. *Id*. at 317, 326. Since this time period, retinal physicians have recognized the underdosing concern. *See*, Stone TW, Hahn P, eds. *ASRS 2019 Preferences and Trends Membership Survey*. Chicago, IL. American Society of Retina Specialists; 2019 at slide 7.

[redacted]

51. In particular, additional injections mean that patients would have a higher risk of contracting a serious intraocular infection from foreign particles being introduced into the eye. REGITC00377092; REGITC00377077; REGITC00378064; REGITC00863006. [redacted] Obviously, the fewer injections associated with EYLEA as compared to LUCENTIS necessarily translates to a lower risk of such infections and endophthalmitis.

52. More frequent injections can also mean more out-of-pocket costs for the patient. [redacted] More frequent injections are especially problematic for patients who require assistance in going to a physician's office, especially in areas where the nearest retinal specialist is far from the patient's home.

53. More frequent office visits would also translate to more clinician time, meaning that the clinician would see fewer individual patients. My practice would also have to store more product, but we only have so much storage capacity. This would be exacerbated by the fact that EYLEA is available in one dosage strength across indications, whereas LUCENTIS requires two dosage strengths. [redacted] Additional office visits would also be needed for roughly 30% of my patients due to their insurance requirements. In particular, the insurance

requirements for certain of my patients require an initial office visit for a clinical evaluation to obtain insurance authorization. A second office visit would then be required for the injection. Thus, for these patients, transitioning to LUCENTIS would require an additional office visit and a delay from their last EYLEA injection.

54. Moreover, given that LUCENTIS requires more frequent injections, Genentech, which manufactures and sells LUCENTIS in the US, would have to significantly increase production of the drug substance if LUCENTIS were to replace the less-frequently injected EYLEA.

55. In addition to the above concerns, I would be very reluctant to switch my patients from EYLEA PFS to another anti-VEGF for no clinically valid reason. Physicians are in the best position to decide what treatment is best for their patients, and they should not be forced to switch from a preferred treatment for a serious medical condition, especially in the midst of a global pandemic.

B. [redacted]

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