REGENERON
SCIENCE TO MEDICINE®

777 Old Saw Mill River Road
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May 1, 2018

Dear Health Care Provider:

In keeping with our commitment to provide the Retina community with the most current information on critical topics related to our product, we would like to provide you with an update regarding post-marketing reports of intraocular inflammation (IOI) following administration of EYLEA® (aflibercept) Injection.

Regeneron regularly monitors the rates of reported IOI. As you are aware, based on our previous communications, earlier this year we updated you and the healthcare community on a relative increase in monthly IOI reports in the United States. Regeneron worked closely with its collaborator, Bayer, to jointly review the worldwide safety information. Bayer had not noted a similar increase in the overall reported rates of IOI outside of the US.

Based on the accumulating information, Regeneron initiated an extensive review of our manufacturing processes and did not identify an association between IOI rates and the EYLEA drug product. However, our analysis identified an association with certain batches of syringes co-packaged in certain lots of final EYLEA cartons that were distributed in the US. While no causative factor could be identified, out of an abundance of caution, on February 28, 2018, Regeneron sent a communication to the ASRS, FDA and Health Care Providers recommending that practitioners not use the identified syringes and offering to exchange the EYLEA kits containing these syringes. In addition, Regeneron stopped distribution of EYLEA kits with the identified syringes.

Historically, based on post-marketing surveillance, the annualized rate of reported IOIs has ranged from 1 to 4 cases per 10,000 vials. The annualized rate of reported IOI amongst the EYLEA kits co-packaged with the identified syringes was 8-12 reports per 10,000 vials, while the rates for the EYLEA kits without the identified syringes that were distributed at the same time generally remained within the historical range. As of April 2018, the overall rate of reported IOI has returned to historical levels of 1-4 reports per 10,000 vials.

We continue our investigation in collaboration with the syringe manufacturer, Becton Dickinson, to identify any potential causative factors. To date, no notable findings have been identified.

We encourage you to continue reporting adverse events by calling 1-855-EYLEA4U (1-855-395-3248). Regeneron is committed to ensuring the safety of patients using its products, and follows established procedures for monitoring the safety of its products.

Sincerely,

Ned Braunstein, MD

Sr. Vice President, Regulatory Affairs and Pharmacovigilance

IMPORTANT SAFETY INFORMATION

- EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

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IMPORTANT SAFETY INFORMATION

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.
- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

IMPORTANT PRESCRIBING INFORMATION

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with

- Neovascular (Wet) Age-related Macular Degeneration (AMD): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not

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demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).

- Macular Edema following Retinal Vein Occlusion (RVO): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly).
- Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in Patients with DME: The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

Please see the full Prescribing Information for EYLEA.

References:

Data on File, Regeneron Pharmaceuticals, Inc. 2018

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