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Update on Intraocular Inflammation (IOI) with syringes packaged in certain lots of EYLEA® (aflibercept) injection

Dear Health Care Provider:

This letter provides an update on reports of Intraocular Inflammation (IOI) following EYLEA® injections.

IOI is a known risk factor of intraocular injections; rates of IOI with EYLEA® during clinical studies are described in the EYLEA® label. The annualized reporting rate of IOI based on post-marketing surveillance has ranged from 1 to 4 cases per 10,000 injections. Additional variability has been seen between individual lots of EYLEA® and from month-to-month. Although overall reporting rates remain within these historical ranges, increased reporting rates were noted with certain recent lots distributed in the US.

In order to determine the cause of this variability, we conducted an extensive review of our manufacturing process including bioreactors, procedures, raw materials, filling sites, distributors, quality standards, as well as external components (eg, syringes and needles included in the EYLEA® kits). We did not identify any association of IOI rates with the EYLEA® drug itself, but an association was seen with certain batches of the syringe included in specific lots of final packaged EYLEA® kits.

Lot numbers of the EYLEA® kits with the affected syringes are provided below.

Out of an abundance of caution, we are taking the following voluntary actions:

- EYLEA® kits with syringes in question will no longer be distributed
- We recommend that practitioners not use the syringes provided in the affected EYLEA® kits
- Affected EYLEA® kits may be exchanged for kits with different syringes by calling 1-855-EYLEA4U (1-855-395-3248) and selecting Option 1 and then Option 3
- We will report on our findings in greater detail at an upcoming scientific meeting

We have communicated our findings and action plan to the FDA and the American Society of Retina Specialists (ASRS) safety committee.

Patient safety is of the utmost importance to Regeneron, and we are committed to keeping the community informed.

Yours truly,



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Lot numbers of EYLEA® kits with affected syringes:

8148200076	8148200092	8148200094	8148200104
8148200090	8148200093	8148200095	8148200105

[Please see accompanying full Prescribing Information.](#)

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.
- 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 ($\geq 5\%$) 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)
- Macular Edema following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in Patients with DME

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