Drug Monograph

Drug/Drug Class:	**Eylea™ (aflibercept) Intravitreal Injection/ Selective Vascular Endothelial Growth Factor Antagonist**
Prepared for:	MO HealthNet
Prepared by:	ACS, A Xerox Company

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Each single-use, glass vial of Eylea® provides 2 mg/0.05 mL (40 mg/mL) of aflibercept solution for intravitreal injection. **Regeneron Pharmaceuticals, Inc.**777 Old Saw Mill River RoadTarrytown, NY 10591-6707
Summary of Findings:	Eylea® is an anti-vascular endothelial growth factor (Anti-VEGF) drug that has demonstrated efficacy for the treatment of patients with wet AMD. Eylea® appears to be similar in efficacy to ranibizumab, but requires less frequent injections. Eylea® received a priority review and a unanimous recommendation for approval by the FDA Dermatologic and Ophthalmic Drugs Advisory Committee. It is also being studied for central retinal vein occlusion, diabetic macular edema, and other eye disorders such as various types of cancer.
Status Recommendation:	☐ Prior Authorization (PA) Required ☒ Open Access ☐ Clinical Edit ☐ PDL Product
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ PA Not Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

Age-related macular degeneration affects the macula and gradually destroys central vision. Central vision provides the fine details that are needed for tasks such as reading and driving. The wet form of AMD includes the growth of abnormal blood vessels that can leak fluid into the macula. This causes the macula to thicken and vision loss. Approximately 1.7 million Americans have the advanced form of this condition, which is the leading cause of blindness in people over the age of 55.

Dosage Form(s) [1]

Each single-use, glass vial of Eylea® provides 2 mg/0.05 mL (40 mg/mL) of aflibercept solution for intravitreal injection.

Manufacturer

Regeneron Pharmaceuticals, Inc.777 Old Saw Mill River Road, Tarrytown, NY 10591-6707

Indication(s) [1]

Eylea® is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD).

Clinical Efficacy[1-6] (mechanism of action/pharmacology, comparative efficacy)

Eylea® is a recombinant fusion protein that is formulated as an iso-osmotic solution for intravitreal administration. It consists of portions of human vascular endothelial growth factor (VEGF) receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG-1. VEGF-A and placental growth factor (PlGF) are angiogenic factors that produce neovascularization and vascular permeability in endothelial cells. VEGF bind to 2 receptor tyrosine kinases: VEGFR-1, present on the surface of endothelial cells and leukocytes, and VEGFR-2, present on the surface of endothelial cells. Activation of these receptors by VEGF-A results in neovascularization and vascular permeability. Eylea® binds to VEGF-A and P1GF, which inhibits kinase activation and prevents neovascularization and enhanced vascular permeability.

Pharmacokinetic data for aflibercept are limited. It is estimated that after intravitreal administration of 2 mg, the mean maximum plasma concentration of free Eylea® is more than 100-fold lower than the concentration required to half-maximally bind systemic VEGF. The volume of distribution of free Eylea® following IV administration is approximately 6 L, and the terminal elimination half-life is approximately 5 to 6 days. Eylea® is eliminated through both

target-mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis.

The approval of Eylea® was primarily based upon two randomized, double-masked, active-controlled clinical trials (VIEW1, VIEW2) involving 2412 patients with wet AMD. Patients received either Eylea® or ranibizumab, with a primary endpoint of visual acuity after one year of treatment. Results from the studies showed that Eylea® was as effective as ranibizumab in maintaining or improving visual acuity.

STUDY DESIGN	Two multicenter, randomized, double-masked, active-controlled clinical trials (n=2412).
INCLUSION CRITERIA	Adult patients with wet AMD.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) Eylea 2 mg every 8 weeks following 3 initial monthly doses (Eylea® 2 mg Q8); 2) Eylea® 2 mg every 4 weeks (Eylea® 2 mg Q4); 3) Eylea® 0.5 mg every 4 weeks (Eylea® 0.5 mg Q4); or 4) ranibizumab 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4). Patient ages ranged from 49 to 99 years, with a mean of 76 years. In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, which was defined as losing fewer than 15 letters of visual acuity at week 52 compared with baseline.
RESULTS	Both the Eylea® 2 mg Q8 and 2 mg Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group. In VIEW 1, the proportion of patients who maintained visual acuity (< 15 letters of best corrected visual acuity (BCVA)) at week 52 was 94%, 95%, and 94% for Eylea® 2 mg Q8, Eylea® 2 mg Q4, and ranibizumab 0.5 mg Q4, respectively. In VIEW 2, the results were 95%, 95%, and 95%, respectively, for the same treatment groups.
SAFETY	The most common adverse reactions (>= 5%) with Eylea® were conjunctival hemorrhage, eye pain, cataracts, vitreous detachment, vitreous floaters, and increased intraocular pressure.

Contraindications[1]

- Patients with ocular or periocular infections.
- Hypersensitivity to any product components.
- Active intraocular inflammation.

Warnings and Precautions[1]

- Endophthalmitis and retinal detachments may occur; patients should report any symptoms suggestive of endophthalmitis or retinal detachment without delay; manage appropriately.
- Increases in intraocular pressure have occurred within 60 minutes of an injection.
- Arterial thromboembolic events (ATEs) are a potential risk for intravitreal VEGF inhibitors; ATEs include nonfatal stroke or myocardial infarction, and vascular death (including of unknown cause).

Adverse Effects[1]

Adverse Reactions	**Eylea® (N=1824)**	**Active Control (ranibizumab)(N=595)**
Conjunctival hemorrhage	**25%**	**28%**
Eye pain	**9%**	**9%**
Cataract	**7%**	**7%**
Vitreous detachment	**6%**	**6%**
Vitreous floaters	**6%**	**7%**
Intraocular pressure increased	**5%**	**7%**
Conjunctival hyperemia	**4%**	**8%**
Corneal erosion	**4%**	**5%**
Detachment of the retinal pigment epithelium	**3%**	**3%**
Injection site pain	**3%**	**3%**
Foreign body sensation in eyes	**3%**	**4%**
Lacrimation increased	**3%**	**1%**
Vision blurred	**2%**	**2%**
Retinal pigment epithelium tear	**2%**	**1%**
Injection site hemorrhage	**1%**	**2%**
Eyelid edema	**1%**	**2%**
Corneal edema	**1%**	**1%**

Drug Interactions[1]

- Drug interaction studies have not been conducted with aflibercept.

Dosage and Administration[1]

The recommended dose for Eylea® is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg(0.05 mL) via intravitreal injection once every 8 weeks (2 months).Although Eylea® may be dosed as frequently as 2 mg every4 weeks (monthly), additional efficacy was not demonstrated when Eylea® was dosed every 4 weeks compared to every 8 weeks

Cost Comparisons (at commonly used dosages)

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	COST/ VIAL
Aflibercept Injection	Eylea®	Regeneron	2 mg/0.05 mL, single-use vial	$ 1842.60*
Ranibizumab Injection	Lucentis®	Genentech	10 mg/mL, single-use vial	$ 1942.20**

*Wholesale Acquisition Cost
** Missouri Maximum Allowable Cost

Conclusion

Eylea® is an anti-VEGF drug that has demonstrated efficacy for the treatment of patients with wet AMD. Aflibercept appears to be similar in efficacy to ranibizumab, but requires less frequent injections. Clinical comparisons with other agents used to treat wet AMD are not available. Aflibercept received a priority review and a unanimous recommendation for approval by the FDA Dermatologic and Ophthalmic Drugs Advisory Committee. It is also being studied for central retinal vein occlusion, diabetic macular edema, and other eye disorders such as various types of cancer.

Recommendation

MO HealthNet Division recommends Open Access status for this product.

References

1. Product Information: Eylea™, aflibercept intravitreal injection. Regeneron Pharmaceuticals, Inc., Tarrytown, NY, 11/2011.
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3. Brown DM, Heier JS, Ciulla T et al: CLEAR-IT 2 Investigators: Primary endpoint results of a phase II study of vascular endothelial growth factor trap-eye in wet age-related macular degeneration. Ophthalmology 2011; 118(6):1089-1097.
4. Heier JS, Boyer D, Nguyen QD et al: CLEAR-IT 2 Investigators: The 1-year results of CLEAR-IT 2, a phase 2 study of vascular endothelial growth factor trap-eye dosed as needed after 12-week fixed dosing. Ophthalmology 2011; 118(6):1098-1106.
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6. Dixon JA, Oliver SC, Olson JL et al: VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration. Expert Opin Investig Drugs 2009; 18(10):1573-1580.

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