U.S. FOOD & DRUG ADMINISTRATION

Eylea (aflibercept)
Treatment of Retinopathy of Prematurity (ROP)

FDA Presentation

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CDER Mission

- The Mission of the Center for Drug Evaluation and Research is to ensure that safe and effective drugs are available to improve the health of people in the United States

Unmet Need

- There are no approved pharmacologic treatments for ROP.

FDA's Pediatric Tools Stick and Carrot

- Potential requirements based on PREA
- Potential incentives based on BPCA

PREA=Pediatric Research Equity Act

BPCA=Best Pharmaceuticals for Children Act

Potential requirements based on PREA

- PREA gives authority to require pediatric studies in certain drugs and biological products.

- The goal of the studies is to obtain pediatric labeling for the product.

Potential incentives based on BPCA

- BPCA provides an incentive of additional marketing exclusivity to sponsors who voluntarily complete pediatric clinical studies outlined in a Written Request issued by FDA.

Requirements not an option

- Requirement waived for current Eylea indications (nAMD, RVO, DME, DR) because they do not occur in pediatric patients.

- FDA granted orphan designation (July23, 2019) of aflibercept for the treatment of ROP.

- Orphan Indications exempt from PREA.

Pediatric Written Requests

- Based on Section 505A of the Federal Food, Drug, and Cosmetic Act, as amended by the Food and Drug Administration Amendments Act of 2007, and pursuant to section 351(m) of the Public Health Service Act, as amended by the Biologics Price Competition and Innovation Act of 2009, the FDA may issue a formal Written Request to obtain needed pediatric information.

Written Request Issued

- June 4, 2019, to obtain needed pediatric information on aflibercept, the FDA issued a formal Written Request for studies to investigate the potential use of aflibercept in the treatment of ROP.

Two Studies Requested

- The primary objective of the studies is to evaluate the efficacy, safety, and tolerability of intravitreal aflibercept in patients with ROP.

- The protocols and statistical analysis plans must be submitted to and agreed upon by the Division.

Study 1

- Randomized, parallel group, controlled study of at least 52 weeks duration with a five-year follow-up, including an assessment of retinal photographs.

- Submission of Week 52 data is required to meet the terms of the Written Request. Five-year follow up must be submitted to the Agency but is not required to meet the terms of the Written Request.

Study 2

- Randomized, parallel group, controlled study of at least 52 weeks duration with a five-year follow-up, including an assessment of retinal photographs.

- Submission of Week 52 data is required to meet the terms of the Written Request. Five-year follow up must be submitted to the Agency but is not required to meet the terms of the Written Request.

Design

- Study design may be either a superiority design or a non-inferiority design compared to an established standard of care.

- Statistical analysis plans must be agreed upon by the Division.

- Demographic characteristics and adverse experiences should be summarized descriptively and compared for each treatment group.

Primary Endpoint

- Absence of active ROP and absence of unfavorable structural outcomes at Week 52 following birth (e.g., retinal detachment) and must be assessed by visualization of the retina (photographic and/or directly by investigators)

Labeling

- Must submit proposed pediatric labeling to incorporate the findings of the studies.

- Regardless of whether the studies demonstrate that aflibercept injection is safe, pure, and potent, or whether such study results are inconclusive in the studied pediatric populations, the labeling must include information about the results of the studies.

BLA 125387 SUPPLEMENT 75

Supplemental Application Submitted on August 11, 2022

Contents of Supplement

- Clinical Study 20090 and Study 20275
  - Firefleye and Firefleye Next
- Clinical Study VGFTeROP-1920
  - Butterfleye and Butterfleye Next
- Labeling

Rationale Control Arm

- Laser treatment considered a viable alternative to Anti-VEGF
- Laser treatment considered equivalent to Cryo treatment and more widely used
- Efficacy estimates available from RAINBOW study

Previously Reported Outcomes

- Natural history*: 55%
- Cryotherapy Treatment*: 75%
- Laser Treatment**: 66%
- Anti-VEGF**: 80-88%

*Multicenter Trial of Cryotherapy for Retinopathy of Prematurity. Arch Ophth. 1990; 108:1408-1416.

** Stahl A, Lepore D, Fielder A, et al. Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial. Lancet. 2019. 394:1551-1559. http://dx.doi.org/10.1016/ S0140-6736(19)31344-3

Non-inferiority Margin

- Non-inferiority Margin Set as: ±5%

Results of Primary Endpoint

FIREFLEYE BAY 86-5321/ 20090 & 20275			**Difference (95% CI)**
Aflibercept	(N=75)	59/75 (79%)	-1.9% (-17%, 13%)
Laser	(N=38)	31/38 (82%)	

BUTTERFLEYE VGFTe-ROP-1920			**Difference (95% CI)**
Aflibercept	(N=93)	74/93 (80%)	1.8% (-16%, 19%)
Laser	(N=27)	21/27 (78%)	

Fails to meet the 5% non-inferiority margin

Neither trial supports the prespecified hypothesis.

Potential Reasons

- Underpowered because power calculations were based on different efficacy rates.
- Population mix between Zone 1 and Zone 2 different than expected.
- Use of photographs to ensure adequate laser treatment

Efficacy consistent with Laser or Cryotherapy and superior to Natural History

Multicenter Trial of Cryotherapy	
Natural History	55%
Cryotherapy	75%
FIREFLEYE	
Aflibercept	79%
Laser	82%
BUTTERFLEYE	
Aflibercept	80%
Laser	78%

Proposed Labeling

- Indication
- Dosing and Administration
- Adverse Events
- Pediatric Use
- Pharmacodynamics
- Pharmacokinetics
- Clinical Trials

Indication

- Treatment of Retinopathy of Prematurity

- Added new indication

Dosing and Administration

The recommended dose for EYLEA is 0.4 mg (0.01 mL or 10 microliters) administered by intravitreal injection. Treatment is initiated with a single injection per eligible eye and may be given bilaterally on the same day. In total, up to 3 injections per eye may be administered from treatment initiation ~~up to one year of chronological age, if there are signs of disease activity~~. The treatment interval between doses injected into the same eye should be at least ~~4 weeks (at least~~ 2~~8~~5 days) ~~[see Clinical Studies (14.6)].~~

- There is no reason why injections must be within 1 year if otherwise indicated.
- 28 Day limit is arbitrary, 25 Day limit allows flexibility in dosing schedule.
- Clinical Studies section does not appear to add additional information concerning dosing.

Dosing and Administration

The EYLEA pre-filled glass syringe is sterile and for single use only. **Do not** use the EYLEA pre-filled syringe for the treatment of ROP.

- Use of pre-filled syringe may increase the risk of a dosing error because the prefilled syringe contains 5 times the dose for ROP.
- It may be better to state what should be used.

Dosing and Administration

Administration in pre-term infants with ROP:

Follow steps 1-10 listed above.

11.To eliminate all of the bubbles and to expel excess drug, SLOWLY depress the plunger rod so that the plunger edge aligns with the line that marks **0.01 mL** on the syringe (see Figure 13a and Figure 13b).

Figure 13a:

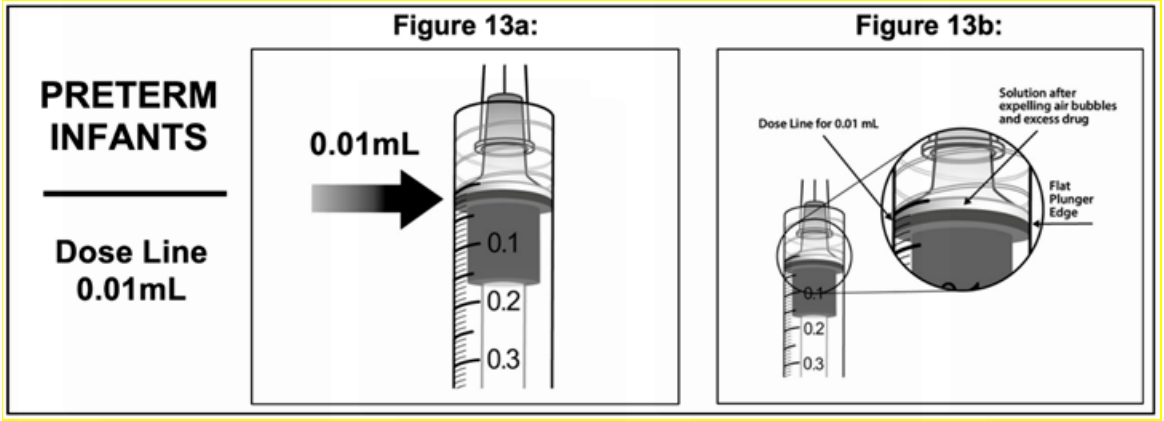

Figure 13b:

- Describes dosing.

Dosing and Administration

For the treatment of ROP, the injection needle should be inserted into the eye 1 mm from the limbus with the needle pointing towards the optic nerve.

- Site of injection noted to be different than Adult dosing

Adverse Reactions

Retinopathy of Prematurity (ROP)

The data described below reflect exposure to EYLEA in 168 pre-term infants with ROP randomized to EYLEA and treated with the 0.4 mg dose in 2 clinical studies (BUTTERFLEYE and FIREFLEYE/FIREFLEYE NEXT) from time of first administration up to 52 weeks of chronological age [see Clinical Studies (14.6)]. Adverse reactions established for adult indications are considered applicable to pre-term infants with ROP, though not all were observed in the ~~Phase 3~~clinical studies.

Table 4: Adverse Reactions in ROP Studies

Adverse Reactions	**Baseline to 52 weeks of chronological age** BUTTERFLEYE		**Baseline to 52 weeks of chronological age** FIREFLEYE/FIREFLEYE NEXT	
	EYLEA (N=93)	**Laser (N=27)**	**EYLEA (N=75)**	**Laser (N=28)**
Retinal detachment	6~~.5~~%	7~~.4~~%	5~~.3~~%	5~~.3~~%
Conjunctival hemorrhage	5~~.4~~%	0%	5~~.3~~%	0%
Injection site hemorrhage	0%	0%	4~~.0~~%	0%
Intraocular pressure increased	0%	0%	4~~.0~~%	0%
Corneal epithelium defect	1~~.1~~%	0%	0%	0%
Eyelid edema	0%	~~3.7~~4%	~~2.7~~3%	~~7.9~~8%
Corneal edema	0%	0%	1~~.3~~%	~~2.6~~3%
Lenticular Opacities	0%	0%	1~~.3~~%	0%

- Percentages Rounded to account for limited significant figures

Pediatric Use

The safety and effectiveness of EYLEA have been demonstrated in pre-term infants with ROP.

Two ~~Phase 3~~, randomized, open-label, controlled studies while demonstrating a clinical course better than the expected natural history in untreated subjects, ~~were conducted to~~ failed to demonstrate that ~~evaluate the safety and effectiveness of~~ EYLEA ~~compared to~~ was non inferior to laser photocoagulation in ~~245~~ the treatment of pre-term infants with ROP ~~until 52 weeks of chronological age~~ [see Dosage and Administration (2.6), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.6)].

- Rationale for approving the indication explained

Pharmacodynamics

~~**Retinopathy of Prematurity (ROP)**~~

~~An exploratory PK/PD analysis showed no relationship between systemic aflibercept concentrations and pharmacodynamic effects on blood pressure.~~

- Statement does not provide useful clinical information

Pharmacokinetics

Pediatric Patients

Pharmacokinetics of aflibercept were evaluated in pre-term infants with ROP at a dose of 0.4 mg aflibercept (per eye) administered unilaterally or bilaterally. In the BUTTERFLEYE study, mean concentrations of free aflibercept in plasma declined from a maximum of 0.583 mcg/mL at Day 1 to 0.0406 mcg/mL at Day 28 in bilaterally treated patients.

In the FIREFLEYE/~~FIREFLEYE NEXT~~ study, mean concentrations of free aflibercept in plasma for all patients (bilateral and unilateral administration combined) declined from a maximum of 0.481 mcg/mL at Day 1 to 0.13 mcg/mL at Day 28. Concentrations of free aflibercept in plasma subsequently declined to values below or close to the lower limit of quantitation within approximately 8 weeks.

- FIREFLEYE NEXT did not contribute to the Pharmacokinetics

Immunogenicity

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. Similarly, in pediatric ROP studies, after unilateral or bilateral dosing, antibodies to EYLEA were detected in less than 1% of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity. ~~In the pediatric ROP studies, after unilateral or bilateral dosing with EYLEA 0.4 mg, antibodies to EYLEA were detected in less than 1% of patients for up to 12 weeks. Because of the low occurrence of ADA, the effect of these antibodies on the pharmacokinetics, safety, or effectiveness of aflibercept 0.4 mg per eye is unknown.~~

- Reworded to describe that the findings in Pediatrics are the same as Adults.

Clinical Studies

Efficacy and safety data of EYLEA in ROP are derived from the BUTTERFLEYE and FIREFLEYE/FIREFLEYE NEXT studies. Both BUTTERFLEYE and FIREFLEYE studies assessed the efficacy, safety and tolerability of EYLEA in randomized, 2-arm, open-label, parallel-group studies in pre-term infants with ROP in comparison to laser photocoagulation therapy (laser). Patients received study treatment at baseline per eligible eye. Additional treatment (re-treatment) and/or rescue treatment, if needed, was administered based on pre-specified criteria. FIREFLEYE NEXT was an observational follow-up Phase 3, multi center study which evaluated the Week 52 safety outcomes and visual function of patients included and treated in the FIREFLEYE study.

- Redundancy of trials reduced

Clinical Studies

Eligible patients had a maximum gestational age at birth of 32 weeks or a maximum birth weight of 1500 g, had to weigh >800 g on the day of treatment and had treatment-naïve ROP classified according to the International Classification for Retinopathy of Prematurity (IC-ROP 2005) in at least one eye with one of the following retinal findings:

ROP Zone 1 Stage 1+, 2+, 3 or 3+, or
ROP Zone II Stage 2+ or 3+, or
AP-ROP (aggressive posterior ROP)

The primary efficacy endpoint of each study was the proportion of patients with absence of active ROP and unfavorable structural outcomes (retinal detachment, macular dragging, macular fold, retrolental opacity) at week 52 of chronological age.

- Redundancy of trials reduced

Clinical Studies

In BUTTERFLEYE, patients were randomized in a 3:1 ratio to receive 1 of 2 treatment regimens: 1) EYLEA 0.4 mg at baseline and if required, up to 2 additional injections and 2) laser photocoagulation in each eye at baseline and if required, retreatment. In FIREFLEYE, patients were randomized to the same two treatments, but in a 2:1 ratio. Rescue treatment was administered if required, per pre specified criteria. In both studies, greater than 92% of all treated patients in the aflibercept group received bilateral injections during the study.

- Differences in trials described and redundancy of trials reduced

Clinical Studies

Results

Results from week 52 of chronological age in the BUTTERFLEYE and FIREFLEYE/FIREFLEYE NEXT studies are shown in Table 12 below. EYLEA was not demonstrated to be non inferior to Laser treatment.

Table 12: Efficacy Outcomes at Week 52 Chronological Age in BUTTERFLEYE and FIREFLEYE/FIREFLEYE NEXT Studies

Full Analysis Set	BUTTERFLEYE		FIREFLEYE	
	EYLEA	Laser	EYLEA	Laser
Efficacy Outcomes	N=93	N=27	N=75	N=38
Proportion of patients with absence of active ROP and unfavorable structural outcomes (%)	80%	78%	79%	82%
Adjusted Difference[b] (%) (95.1% CI)	1.8% (-16, 19)		-1.9% (-17, 13)	

- Percentages Rounded to account for limited significant figures
- Secondary endpoints removed

Questions


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