PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrEYLEA® HD

Aflibercept injection

Single Use Vials for the Treatment of a Single Eye

8 mg / 0.07 mL Solution for Intravitreal Injection

Ophthalmological / Antineovascularization agent

ATC Code: S01LA05

Bayer Inc.
2920 Matheson Boulevard East
Mississauga, Ontario
L4W 5R6

http://www.bayer.ca

Submission Control Number: 287329

Date of Initial Authorization:
November 08, 2013

Date of Revision:

August 13, 2024

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

EYLEA HD (aflibercept injection) is indicated for:

- the treatment of neovascular (wet) age-related macular degeneration (AMD)
- the treatment of diabetic macular edema (DME)

1.1 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and effectiveness of EYLEA HD in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies of EYLEA HD include participants 65 years of age and older. No clinically significant differences in efficacy or safety were seen with increasing age in these studies.

2 CONTRAINDICATIONS

- Patients who are hypersensitive to this drug, to any ingredient in the formulation, or to any component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section.
- Patients with ocular or periocular infection
- Patients with active intraocular inflammation

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY.
- The Eylea HD vial is for **single-use only**.
- The vial contents should not be split or further compounded. Use of more than one injection from a vial may increase the risk of contamination and subsequent infection.
- Eylea HD must only be administered by a qualified physician experienced in administering intravitreal injections.
- Aflibercept at a dose of 8 mg must only be administered using Eylea HD. Aflibercept at a dose of 2 mg must only be administered using Eylea.

4.2 Recommended Dose and Dosage Adjustment

Treatment of wet AMD

Eylea HD 8 mg (0.07 mL) is administered by intravitreal injection every month (4 weeks +/- 1 week) for the first 3 consecutive doses, followed by 8 mg (0.07 mL) every 8 to 16 weeks (+/- 1 week) based on the physician's judgement of visual and anatomic outcomes (see 14 CLINICAL TRIALS).

Patients should be evaluated regularly. Monitoring visits and treatment interval should be based on the patient's status and at the physician's discretion.

Treatment of DME

Eylea HD 8 mg (0.07 mL) is administered by intravitreal injection every month (4 weeks +/- 1 week) for the first 3 consecutive doses, followed by 8 mg (0.07 mL) every 8 to 16 weeks (+/- 1 week) based on the physician's judgement of visual and anatomic outcomes (see 14 CLINICAL TRIALS).

Patients should be evaluated regularly. Monitoring visits and treatment interval should be based on the patient's status and at the physician's discretion.

Special Populations

Hepatic and/or renal impairment: No specific studies in patients with hepatic and/or renal impairment were conducted with Eylea HD.

Geriatrics (≥ 65 years of age): No special dosing considerations are needed in elderly populations.

Pediatrics (< 18 years of age): The safety and efficacy of Eylea HD have not been established in pediatric patients. Health Canada has not authorized an indication for pediatric use.

4.4 Administration

Intravitreal injections must be carried out by a qualified physician experienced in administering intravitreal injections, and according to medical standards and under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). The peri-ocular skin, eyelid and ocular surface should be disinfected. Adequate anesthesia and a topical broad spectrum microbicide should be used prior to the injection.

Prior to administration visually inspect the solution for injection. Do not use the vial if particulates, cloudiness, or discoloration are visible.

For the intravitreal injection a 30 G x ½ inch injection needle (not supplied) should be used.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available.

Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis, retinal detachment or tear, cataract or increased intraocular pressure (eg, eye pain, redness of the eye, photophobia, blurring or loss of vision) without delay.

THE VIAL IS FOR SINGLE-USE ONLY. EACH VIAL IS TO BE USED ONLY FOR THE TREATMENT OF ONE EYE WITH 8 MG / 0.07 ML OF EYLEA HD.

AFTER INJECTION, ANY UNUSED PRODUCT OR WASTE MATERIAL MUST BE DISCARDED.

Prior to usage, the unopened vial of Eylea HD may be stored at room temperature (25°C) for up to 24 hours. After opening the vial, proceed under aseptic conditions.

To prepare Eylea HD for intravitreal injection, please adhere to the following instructions:

Filter needle:

Blunt filter (fill) needle, **not** for skin injection. Do **not** autoclave the blunt filter (fill) needle. The filter needle is non-pyrogenic. Do **not** use it if individual packaging is damaged. Discard the used blunt filter

(fill) needle in approved sharps collector. **Caution:** Re-use of the filter needle may lead to infection or other illness/injury.

1. Remove the protective plastic cap from the vial (see Figure 1).

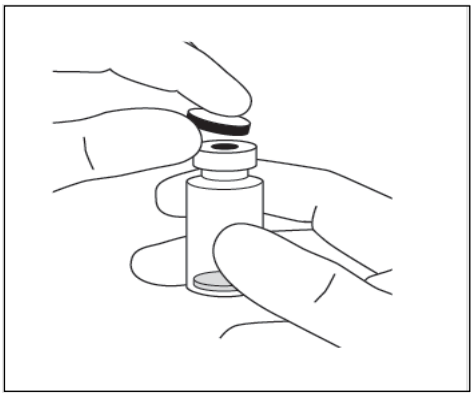


Figure 1

2. Clean the top of the vial with an alcohol wipe (see Figure 2)

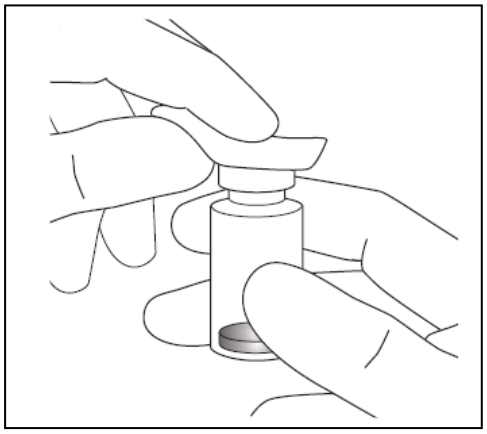


Figure 2

3. Remove the 18 G, 5-micron filter needle supplied in the carton from its pouch. Attach the filter needle to a 1-mL sterile, Luer-lock syringe (not supplied) by twisting it onto the Luer lock syringe tip (see Figure 3).

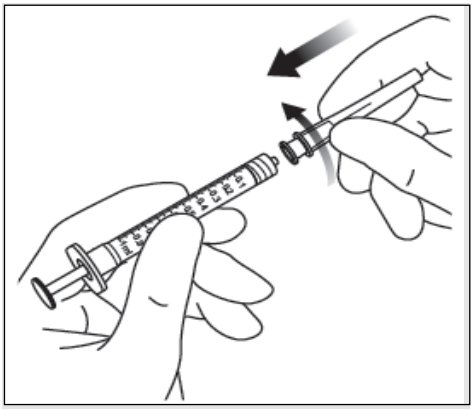


Figure 3

4. Push the filter needle into the centre of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom edge of the vial.

5. Using aseptic technique withdraw all of the Eylea HD vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid (see Figure 4 and Figure 5).

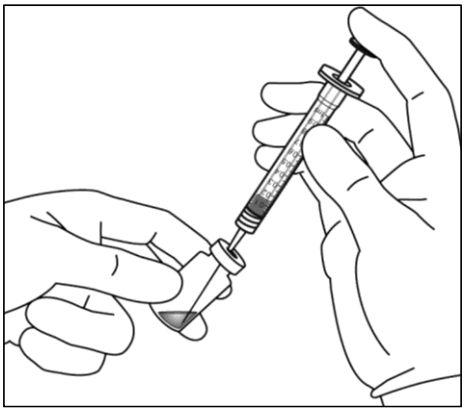


Figure 4

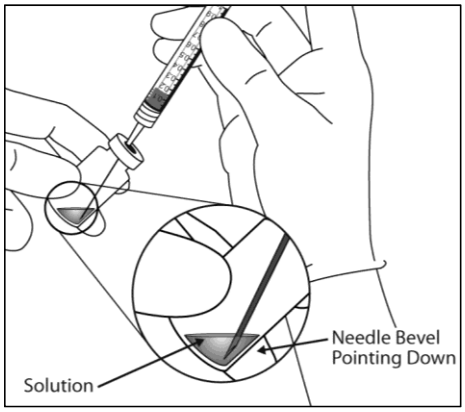


Figure 5

6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle. After injection, discard any unused product or waste material in accordance with local regulations.

7. Remove the filter needle from the syringe and properly dispose of the filter needle.

   Note: Filter needle is **not** to be used for intravitreal injection.

8. Using aseptic technique, attach a 30 G x ½ inch injection needle (not supplied) to the syringe by firmly twisting the injection needle onto the Luer-lock syringe tip (see Figure 6).

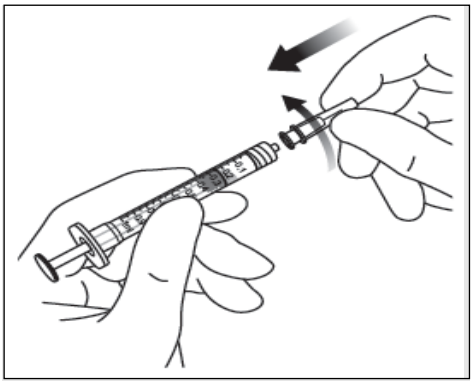


Figure 6

9. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, **gently tap** the syringe with your finger until the bubbles rise to the top (see Figure 7).

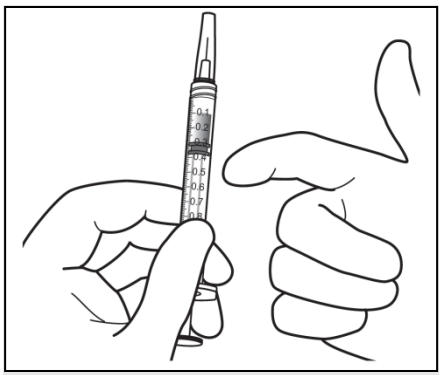


Figure 7

10. To eliminate all of the bubbles and to expel excess drug, **slowly** depress the plunger so that the flat plunger edge aligns with the line that marks **0.07 mL** on the syringe.

    See Figure 8 and Figure 9.

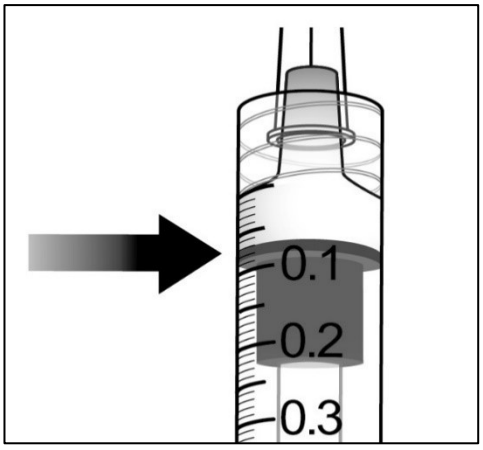


Figure 8

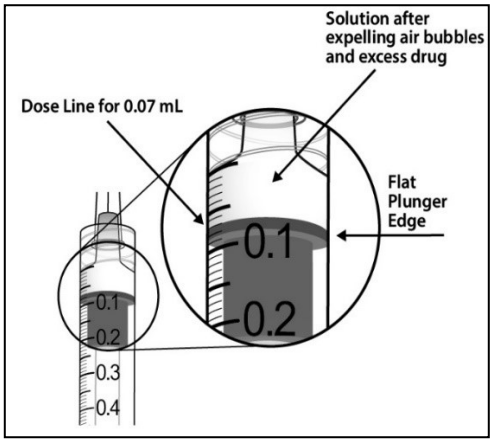


Figure 9

4.5 Missed Dose

If a planned injection of Eylea HD is missed, reset a new appointment for an examination and injection as soon as possible. Reset the dose schedule to administer the next sequential dose after the missed dose is administered.

5 OVERDOSAGE

Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of an overdose, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated (see 7 WARNINGS AND PRECAUTIONS and 12 SPECIAL HANDLING INSTRUCTIONS).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravitreal Injection	Solution / 8 mg / 0.07 mL	L-arginine monohydrochloride; L-histidine; L-histidine monohydrochloride monohydrate; polysorbate 20; sucrose and water for injection

Eylea HD is provided as a sterile, clear to slightly opalescent, colourless to pale yellow, iso-osmotic, aqueous solution containing L-arginine monohydrochloride; L-histidine; L-histidine monohydrochloride monohydrate; polysorbate 20; sucrose and water for injection.

One millilitre solution for intravitreal injection contains 114.3 mg aflibercept.

Each carton includes a type I glass vial containing a nominal fill volume of 0.263 mL solution for intravitreal injection with an elastomeric rubber stopper, and an 18 G filter needle.

Each vial provides a usable amount to deliver a single dose of 0.07 mL containing 8 mg aflibercept.

7 WARNINGS AND PRECAUTIONS

General

Aflibercept at a dose of 8 mg must only be provided using Eylea HD (8 mg / 0.07 mL). Aflibercept at a dose of 2 mg must only be provided using Eylea (2 mg / 0.05 mL).

Driving and Operating Machinery

Patients may experience temporary visual disturbances after an intravitreal injection with Eylea HD and the associated eye examinations. They should not drive or use machines until visual function has recovered sufficiently.

Immune

Hypersensitivity

As with all therapeutic proteins, there is a risk of hypersensitivity reactions including anaphylaxis. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation. Patients should be instructed to report any symptoms of anaphylaxis, allergic reactions or intraocular inflammation (e.g., pain, photophobia, or redness, which, although non-specific, should also be assessed as potential hypersensitivity reactions).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with Eylea HD.

Immunogenicity was measured in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to Eylea HD in immunoassays, and are highly dependent on the sensitivity and specificity of the assays.

During the 48-week treatment with aflibercept administered IVT, treatment-emergent antibodies to Eylea HD were detected in 1.2% to 3.6% of patients treated for DME and wet AMD.

Ophthalmologic

Endophthalmitis, Retinal detachments and Cataracts

Intravitreal injections, including those with aflibercept, have been associated with endophthalmitis, retinal detachment, retinal tear, retinal pigment epithelium tear, cataract including traumatic cataract, vitreous hemorrhage and hyphema (see 8 ADVERSE REACTIONS). The proper aseptic injection technique must always be used when administering Eylea HD (see 4.4 Administration). Patients should be instructed to report any symptoms suggestive of any event listed above without delay and should be managed appropriately.

Increase in Intraocular Pressure (IOP)

Transient increases in intraocular pressure (IOP) have been observed within 60 minutes of an intravitreal injection, including with Eylea HD (see 8 ADVERSE REACTIONS). Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors.

In all cases, both intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately.

Eylea HD has not been tested in patients with poorly controlled glaucoma.

Other

As with other intravitreal anti-VEGF treatments, treatment should be withheld and resumed only when considered appropriate in cases of:

- An IOP of ≥ 30 mmHg
- Within the previous or next 28 days in the event of a performed or planned intraocular surgery
- A retinal break. The treatment should not be resumed until the break is adequately repaired

There is only limited experience in the treatment of subjects with DME due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy.

Eylea HD has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with Eylea HD in diabetic patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients.

In the Eylea HD clinical trials of AMD and DME, only one eye per patient was treated with Eylea HD (see 14 CLINICAL TRIALS).

The safety and efficacy of Eylea HD therapy administered to both eyes concurrently or consecutively have not been studied. If bilateral treatment is performed at the same time, this could lead to an increased systemic exposure, which could increase the risk of systemic adverse events. (see 16 NON-CLINICAL TOXICOLOGY).

Reproductive Health: Female and Male Potential

Women of childbearing potential have to use effective contraception during treatment and for at least 4 months after the last intravitreal injection of Eylea HD (see 7.1.1 Pregnant Women).

Fertility

There are no fertility data in humans. Results from animal studies with high systemic exposure indicate that aflibercept can impair male and female fertility (see 16 NON-CLINICAL TOXICOLOGY).

Systemic Effects

Thromboembolic Events

Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a potential risk of ATEs following intravitreal use of VEGF inhibitors, including Eylea HD.

ATEs, as defined by the Antiplatelet Trialists' Collaboration (APTC) criteria, include nonfatal myocardial infarction, nonfatal stroke, or vascular death (including deaths of unknown cause). There are limited data on safety in the treatment of patients with DME with a history of stroke or transient ischemic attacks or myocardial infarction within the last 6 months.

A low incidence rate of APTC ATEs was observed in the Eylea HD clinical studies in patients with wet AMD (PULSAR) and DME (PHOTON) (0.4% and 4.5%, respectively). Across indications no notable difference between the patient groups treated with Eylea HD and the comparator group treated with Eylea were observed.

Non-ocular Hemorrhages

Non-ocular hemorrhages have been reported following intravitreal injection of VEGF inhibitors, including aflibercept, and there is a theoretical risk that these may relate to VEGF inhibition.

7.1 Special Populations

7.1.1 Pregnant Women

There are no data on the use of aflibercept in pregnant women. Studies in animals have shown reproductive toxicity after systemic administration including fetal loss and severe embryofetal malformations (see 16 NON-CLINICAL TOXICOLOGY). Eylea HD should not be used during pregnancy.

7.1.2 Breast-feeding

It is not known whether aflibercept is excreted in human milk. A risk to the breast-fed child cannot be excluded. Eylea HD is not recommended during breast-feeding. A decision must be made whether to discontinue breast-feeding or to postpone, if feasible, therapy with Eylea HD.

7.1.3 Pediatrics

Pediatric Use (< 18 years of age): The safety and effectiveness of Eylea HD in pediatric patients have not been established.

7.1.4 Geriatrics

In the wet AMD Phase III study, approximately 89% of the patients randomized to treatment with Eylea HD or Eylea were ≥65 years of age and approximately 51% were ≥75 years of age.

In the DME Phase II/III study, approximately 44% of the patients randomized to treatment with Eylea HD or Eylea were ≥65 years of age, and approximately 11% were ≥75 years of age.

No clinically significant differences in efficacy or safety were seen with increasing age in these studies.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Treatment of wet AMD

A total of 1009 (Eylea HD n = 673; Eylea n = 336) patients with up to 60 weeks exposure to Eylea HD or Eylea constituted the safety population in the double-blind, active-controlled study, PULSAR (see 14 CLINICAL TRIALS).

Serious adverse reactions related to the injection procedure have occurred in less than 1 in 4,300 intravitreal injections with Eylea HD and included intraocular pressure increased (see 7 WARNINGS AND PRECAUTIONS).

The ocular serious adverse reactions in patients treated with Eylea HD were retinal detachment (0.4%), intraocular pressure increase (0.3%) and cataract (0.1%).

The most frequently observed adverse reactions in at least 2% of patients treated with Eylea HD were, cataract (4.6%), intraocular pressure increased (3.1%), vitreous floaters (2.7%), vitreous detachment (2.5%), and conjunctival hemorrhage (2.1%) see Table 2.

Treatment of DME

A total of 658 patients (Eylea HD n = 491; Eylea n = 167) with up to 60 weeks exposure to aflibercept constituted the safety population in the double-blind, active-controlled study PHOTON.

Serious adverse reactions related to the injection procedure have occurred in less than 1 in 1,500 intravitreal injections with Eylea HD and included intraocular pressure increased (see 7 WARNINGS AND PRECAUTIONS).

The ocular serious adverse reactions in patients treated with Eylea HD were cataract subcapsular (0.2%), intraocular pressure increase (0.2%) and retinal detachment (0.2%).

The most frequently observed adverse reactions in at least 2% of patients treated with Eylea HD were vitreous floaters (4.9%), conjunctival hemorrhage (4.3%), vitreous detachment (2.9%), punctate keratitis (2.2%), and eye pain (2.0%), see Table 3.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Treatment of wet AMD

The safety data include all adverse reactions (serious and non-serious) with a reasonable possibility of causality to the injection procedure or medicinal product reported (see Table 2 for baseline to week 60 data).

Table 2: Adverse Reactions with Incidence rate ≥1% in any treatment arm in the Eylea HD wet AMD Phase III study (PULSAR, 60 weeks)

Primary system organ class Preferred term MedDRA Version 25.0	**Eylea HD 8Q12 N= 335 Baseline to Week 60**	**Eylea HD 8Q16 N= 338 Baseline to Week 60**	**Eylea 2Q8 N= 336 Baseline to Week 60**
Eye disorders			
Cataract	5%	4%	4%
Vitreous floaters	1%	4%	4%
Vitreous detachment	2%	3%	2%
Conjunctival hemorrhage	2%	2%	2%
Eye pain	2%	2%	1%
Retinal pigment epithelial tear	2%	1%	1%
Punctate keratitis	<1%	1%	2%
Injury, poisoning and procedural complications			
Corneal abrasion	1%	1%	1%
Investigations			
Intraocular pressure increased	3%	3%	3%

A subject is counted only once within each primary SOC and preferred term.
Ocular adverse drug reactions consider treatment emergent adverse events (TEAEs) in study eye only. TEAE in fellow eye are not considered.
8Q12: Aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals.
8Q16: Aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
2Q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals.

Treatment of DME

The data described in Table 3 reflects exposure to Eylea HD in one randomized, double blind, controlled phase II/III study in 658 (8Q12 n= 328, 8Q16, n= 163; 2Q8: n= 167) patients with up to 60 weeks of exposure to Eylea HD.

Table 3: Adverse Reactions with Incidence rate ≥1% in any treatment arm in the Eylea HD DME Phase II/III study (PHOTON, 60 weeks)

System/Organ Class Preferred Term (MedDRA Version 25.0)	Eylea HD 8Q12 (N= 328)	Eylea HD 8Q16 (N= 163)	Eylea 2Q8 (N= 167)
Eye Disorders			
Vitreous floaters	6%	4%	2%
Conjunctival hemorrhage	4%	4%	4%
Cataract	3%	6%	2%
Vitreous detachment	3%	3%	2%
Punctate keratitis	2%	4%	1%
Eye pain	3%	1%	2%
Vision blurred	1%	1%	2%
Cataract subcapsular	2%	0	1%
Cataract nuclear	1%	1%	1%
Corneal erosion	<1%	1%	0
Injury, Poisoning and Procedural Complications			
Corneal abrasion	1%	1%	1%
Investigations			
Intraocular pressure increased	2%	1%	4%

The percentage was based on the number of patients in each treatment group as denominator. Patients are only counted once in each row but may appear in more than one row.

Ocular adverse drug reactions consider treatment emergent adverse events (TEAEs) in study eye only. TEAEs in the fellow eye are not considered.

2 mg: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals.

8Q12: Aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals.

8Q16: Aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.

8.3 Less Common Clinical Trial Adverse Reactions

Treatment of wet AMD and DME

Less common adverse drug reactions reported in <1% of the patients treated with Eylea HD for up to 60 weeks in the Phase II/III studies (DME and AMD pooled data).

Eye Disorders: cataract cortical, cataract nuclear, cataract subcapsular, conjunctival hyperaemia, corneal abrasion, corneal erosion, corneal edema, detachment of retinal pigment epithelium, eyelid edema, foreign body sensation in eyes, iridocytclitis, iritis, lacrimation increased, retinal detachment, retinal pigment epithelial tear, retinal tear, uveitis, vision blurred, vitritis.

General Disorders and Administration Site Conditions: injection site hemorrhage, injection site pain.

Immune System Disorders: hypersensitivity (includes: pruritus, urticaria, rash)

The following adverse reactions of Eylea are also considered expected with Eylea HD but have not been reported in the studies with Eylea HD: anterior chamber flare, corneal epithelium defect, lenticular opacities, ocular hyperemia, endophthalmitis, hypopyon, cataract traumatic, severe anaphylactic/anaphylactoid reactions.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

There were no hematologic or clinical chemistry ADRs seen in Phase II/III wet AMD and DME studies.

8.5 Post-Market Adverse Reactions

Intraocular inflammation has been reported in association with the use of Eylea during the post-marketing experience i.e., endophthalmitis (infectious and non-infectious), anterior chamber flare, iridocyclitis, uveitis, iritis, vitritis and hypopyon. These were consistent with the findings from the clinical trials.

During the post-marketing period, reports of hypersensitivity included rash, pruritus, urticaria, and isolated cases of severe anaphylactic/anaphylactoid reactions.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal drug interaction studies have been performed with Eylea HD. Eylea HD must not be mixed with other medicinal products.

Adjunctive use of verteporfin photodynamic therapy (PDT) and Eylea HD has not been studied.

The safety and efficacy of wet AMD patients who were previously treated with laser photocoagulation have not been studied.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of pro-angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via 2 receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leukocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularization and excessive vascular permeability which is believed to contribute to vision loss in a variety of ocular diseases.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

10.2 Pharmacodynamics

Treatment of wet AMD

In the Phase III study (PULSAR), at Week 48, the mean change from baseline in central retinal thickness (CRT) (Eylea HD 8Q12 and Eylea HD 8Q16 vs. Eylea 2Q8) was -141.9 and -147.1 microns vs. -126.3 microns.

Treatment of DME

PHOTON Study

In the Phase III study (PHOTON), at Week 48, the mean change from baseline in CRT (Eylea HD 8Q12 and Eylea HD 8Q16 vs. Eylea 2Q8) was -171.65 and -148.30 microns vs. -165.31 microns.

10.3 Pharmacokinetics

Table 4: Summary of observed free aflibercept pharmacokinetic parameters in combined DME and wet AMD populations with dense pharmacokinetic sampling, who received a single unilateral 8 mg intravitreal dose

C_{max} (mg/L)	t_{max} (d)	t_{last} (d)	$AUC_{(0\text{-}28d)}$ (day·mg/L)
0.248 (0.210) n = 50	1.02 (0.147 - 4.03) n = 48	21.0 (2.00 - 32.0) n = 48	1.77 (0.758) n = 44

C_{max} = maximum observed concentration, t_{max} = time of C_{max} , t_{last} = last observed concentration above the lower limit of quantitation, $AUC_{(0\text{-}28d)}$ = area under the concentration-time curve from time zero to 28 days after administration.

C_{max} and $AUC_{(0\text{-}28d)}$ are provided as mean (SD), t_{max} and t_{last} as median (range). Eylea HD is administered directly into the vitreous to exert local effects in the eye.

Absorption:

Following intravitreal administration of aflibercept, a fraction of the administered dose is expected to bind with free endogenous VEGF to form an inactive VEGF: aflibercept complex in the eye. From the ocular space, free and bound aflibercept are slowly absorbed into the systemic circulation where it is predominately observed as the inactive stable complex with VEGF; however, only "free aflibercept" is able to bind endogenous VEGF. Peak observed plasma concentrations (C_{max}) of free aflibercept are reached within 4 days after administration.

Distribution:

Since consistent pharmacokinetics between the wet AMD and DME populations were observed, pharmacokinetic parameters are presented for the two populations combined. Following unilateral intravitreal administration of 8 mg aflibercept, the mean (SD) C_{max} of free aflibercept in plasma was 0.25 (0.21) mg/L, and the median time to maximal observed concentration in plasma was 1 day. The accumulation of free aflibercept in plasma following three initial monthly intravitreal doses was minimal. Subsequently no further accumulation was observed. These data are also supported by population pharmacokinetic analyses.

Metabolism:

As Eylea HD is a protein-based therapeutic, no metabolism studies have been conducted.

Elimination:

Aflibercept is expected to be eliminated through both binding to endogenous VEGF and a slower non-saturable clearance (e.g., proteolysis) mechanism. The median time to reach the last quantifiable concentration of free aflibercept in plasma for 8 mg administered intravitreally was 3 weeks.

Special Populations and Conditions

- **Pediatrics (< 18 years of age)** Wet AMD does not occur in children or adolescents. The safety and efficacy of Eylea HD have not been studied in pediatric patients in the indications wet AMD and DME.
- **Geriatrics (≥ 65 years of age)**: No special considerations are needed.
- **Hepatic Insufficiency**: No specific studies in patients with hepatic impairment were conducted with Eylea HD.
- **Renal Insufficiency** No special studies in patients with renal impairment were conducted with Eylea HD.

The systemic exposures to aflibercept in patients with mild to severe renal impairment were similar to those with normal renal function.

11 STORAGE, STABILITY AND DISPOSAL

Store in a refrigerator (2°C to 8°C). Do not freeze.

Keep the vial in the outer carton in order to protect from light.

12 SPECIAL HANDLING INSTRUCTIONS

Do not use if the package or its components are expired, damaged, or have been tampered with.

For the intravitreal injection, a 30 G x ½ inch injection needle should be used.

THE VIAL IS FOR SINGLE USE IN ONE EYE ONLY.

Check the label on the vial to make sure you have the correct strength.

Prior to administration visually inspect the solution for injection. Do not use the vial if particulates, cloudiness, or discoloration are visible.

Prior to usage, the unopened vial of Eylea HD may be stored at room temperature (25°C) for up to 24 hours. After opening the vial, proceed under aseptic conditions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Aflibercept

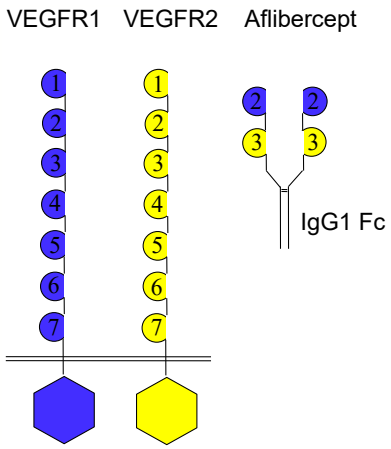
Chemical name: des-432-lysine-[human vascular endothelial growth factor receptor 1-(103-204)-peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig-like C2-type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 C-terminal residues)-peptide (Fc fragment)], (211-211':214-214')-bisdisulfide dimer

Molecular formula: $C_{4318}H_{6788}N_{1164}O_{1304}S_{32}$

Molecular weight: Without glycolysation: 97 kDa

With glycolysation: 115 kDa

Structural formula:



Physicochemical properties: Aflibercept is a dimeric glycoprotein. The Eylea HD solution for intravitreal administration is a sterile, clear to opalescent, colourless to pale yellow, iso-osmotic solution.

pH: Eylea HD solution for intravitreal injection: 5.8

Pharmaceutical standard: In-house standard

Product Characteristics:

Eylea HD (aflibercept injection) is a recombinant fusion protein consisting of portions of human Vascular Endothelial Growth Factor (VEGF) receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and formulated as an iso-osmotic solution for intravitreal administration. Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of Wet AMD

PULSAR Study

The safety and efficacy of Eylea HD (aflibercept injection) was assessed in a Phase 3, randomized, multi-center, double-blind, active-controlled study (PULSAR) in patients with wet AMD. PULSAR was conducted in Canada, Europe, Latin America, Asia and the United States of America. A total of 1009 patients were randomized 1:1:1 ratio to 1 of 3 dosing regimens.

1) Eylea administered at 2 mg every 8 weeks (+/- 1 week) following 3 initial monthly doses (Eylea 2Q8),
2) Eylea HD administered at 8 mg every 12 weeks (+/- 1 week) following 3 initial monthly doses (Eylea HD 8Q12), and
3) Eylea HD administered at 8 mg every 16 weeks (+/- 1 week) after 3 initial monthly doses (Eylea HD 8Q16)

Starting at Week 16, patients in the Eylea HD 8Q12 and 8Q16 groups could be treated as frequently as every 8 weeks (+/- 1 week) based on protocol-defined visual and anatomic outcomes (e.g., decreased visual acuity, increased central subfield thickness, presence of new foveal hemorrhage or new foveal neovascularization, etc.). The minimum interval between injections was 8 weeks (+/- 1 week) in all groups.

Patients in the 8Q12-, 8Q16- and 2Q8-groups who completed week 48 received a median (mean) of 6.0 (6.1), 5.0 (5.2) and 7.0 (6.9) injections, respectively.

Table 5: Summary of Patient Demographics for Eylea HD Clinical Trials in wet AMD

Study#	Trial Design	Dosage, route of administration, and duration	Study Subjects (n)	Mean Age (Range) years	Sex
PULSAR	randomized, multi-center, double-blind, active-controlled	Intravitreal injection following 3 initial monthly doses, • Eylea HD administered at 8 mg every 12 weeks (8Q12), • Eylea HD administered at 8 mg every 16 weeks (8Q16), • Eylea administered at 2 mg every 8 weeks (2Q8).	Eylea HD 8Q12: n=335 Eylea HD 8Q16: n=338 Eylea 2Q8: n=336	74.5 (50 to 96)	Male: 45.5% Female: 54.5%

The primary efficacy endpoint was the mean change from baseline in best corrected visual acuity (BCVA) measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at Week 48.

Treatment with 8Q12 and 8Q16 was shown to be non-inferior to treatment with 2Q8 in terms of the primary efficacy endpoint at Week 48 using the pre-specified non-inferiority margin of 4 letters (Table 6).

Table 6: Efficacy Outcomes at Week 48 from the PULSAR study (wet AMD)

Efficacy Outcomes	Eylea HD 8Q12 (N = 335)	Eylea HD 8Q16 (N = 338)	Eylea 2Q8 (N = 336)
Mean BCVA (SD) at baseline	59.9 (13.4)	60.0 (12.4)	58.9 (14.0)
Change in BCVA from baseline at Week 48 as measured by ETDRS letter score[c]			
Arithmetic mean (SD), observed	6.7 (12.6)	6.2 (11.7)	7.6 (12.2)
LS mean (SE)[a]	6.06 (0.77)	5.89 (0.72)	7.03 (0.74)
Difference in LS means[a, b](95% CI)	-0.97 (-2.87, 0.92)	-1.14 (-2.97, 0.69)	
p-value (one-sided non-inferiority test at a margin of 4 letters) [a, b]	0.0009	0.0011	

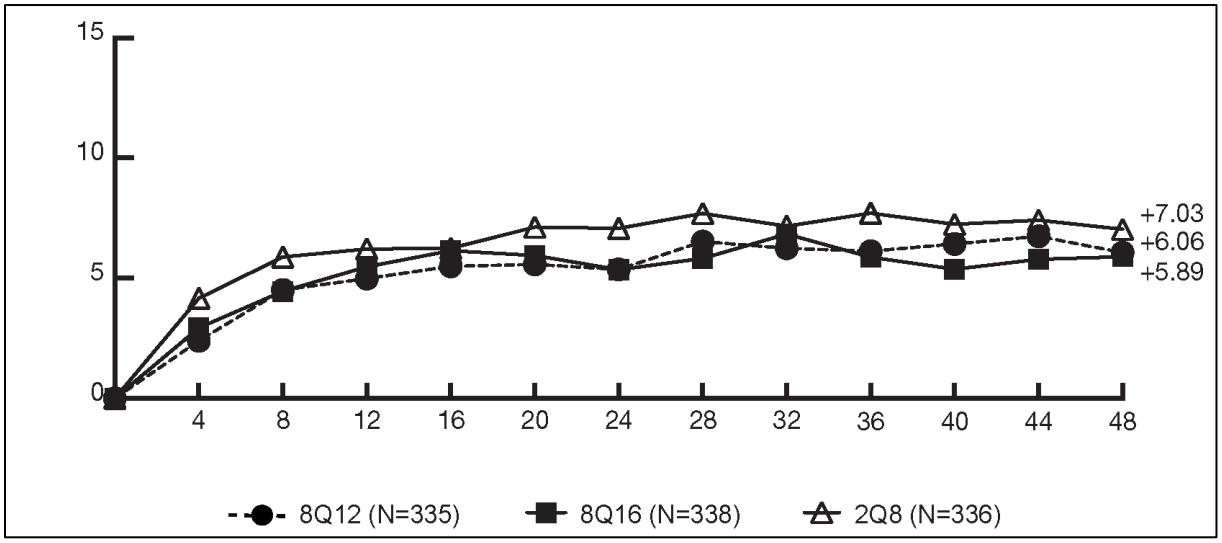
CI: Confidence interval; LS: Least square; SD: Standard deviation; SE: Standard error

a LS mean, CI and p-value based on an MMRM with baseline best corrected visual acuity (BCVA) measurement as covariate, treatment group as factor, visit and stratification variables used for randomization (geographical region, categorical baseline BCVA) as fixed factors as well as terms for the interaction between baseline BCVA and visit and for the interaction between treatment and visit.

b Absolute difference is Eylea HD 8Q12 or 8Q16 groups minus Eylea 2Q8 group, respectively.

c Full Analysis Set

Figure 10: LS mean change in BCVA as measured by ETDRS letter score from baseline through week 48 (Full Analysis Set) in PULSAR study



At week 48, 79.4% of patients in the 8Q12 group were maintained with the 8Q12 treatment interval and 76.6% of patients in the 8Q16 group were maintained with the 8Q16 treatment intervals.

Treatment of DME

PHOTON Study

The safety and efficacy of Eylea HD (aflibercept injection) was assessed in a Phase 2/3, randomized, multi-center, double-blind, active-controlled study (PHOTON) in patients with DME. PHOTON was conducted in Canada, Europe, Japan, United Kingdom and the United States of America. A total of 658 patients were randomized 2:1:1 ratio to 1 of 3 dosing regimens:

1) Eylea HD administered every 12 weeks (+/- 1 week) (8Q12), after 3 initial injections at 4-week intervals
2) Eylea HD administered every 16 weeks (+/- 1 week) (8Q16), after 3 initial injections at 4-week intervals
3) Eylea administered every 8 weeks (+/- 1 week) (2Q8), after 5 initial injections at 4-week intervals

Starting at Week 16, patients in the Eylea HD 8Q12 and 8Q16 groups could be treated as frequently as every 8 weeks (+/- 1 week) based on protocol-defined visual and anatomic outcomes (e.g., decreased visual acuity, increased central subfield thickness, presence of new foveal hemorrhage or new foveal neovascularization, etc.). The minimal interval between injections was 8 weeks (+/- 1 week) in all groups.

Patients in the 8Q12-, 8Q16- and 2Q8-groups who completed week 48 received a median (mean) of 6.0 (6.0), 5.0 (5.0) and 8.0 (7.9) injections, respectively.

Table 7: Summary of Patient Demographics for Eylea HD Clinical Trials in DME

Study	Trial Design	Dosage, route of administration, and duration	Study Patients (n)	Mean Age (Range) years	Sex
PHOTON	randomized, multi-center, double-blind, active-controlled.	Intravitreal injection • Eylea HD administered at 8 mg every 12 weeks following 3 initial monthly injections (Eylea HD 8Q12). • Eylea HD administered at 8 mg every 16 weeks following 3 initial monthly injections (Eylea HD 8Q16). • Eylea administered at 2 mg every 8 weeks following 5 initial monthly injections (Eylea 2Q8).	Eylea HD 8Q12: n= 328 Eylea HD 8Q16: n= 163 Eylea HD 2Q8: n= 167	62.3 (24 to 90)	Male: 60.9 % Female: 39.1 %

The primary efficacy endpoint was the mean change from baseline in best corrected visual acuity (BCVA) measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at Week 48.

Treatment with Eylea HD (both 8Q12- and 8Q16-groups) was shown to be non-inferior to treatment with Eylea (2Q8), in terms of the primary efficacy endpoint at Week 48 using the pre-specified non-inferiority margin of 4 letters (Table 8).

Table 8: Efficacy outcomes at Week 48 from the PHOTON study

Efficacy Outcomes	Eylea HD 8Q12 (N = 328)	Eylea HD 8Q16 (N = 163)	Eylea 2Q8 (N = 167)
Mean BCVA (SD) at baseline	63.6 (10.10)	61.4 (11.76)	61.5 (11.22)
Change in BCVA from baseline at Week 48 as measured by ETDRS letter score[c]			
Arithmetic mean (SD), observed	8.77 (8.95)	7.86 (8.38)	9.21 (8.99)
LS mean (SE) [a]	8.10 (0.61)	7.23 (0.71)	8.67 (0.73)
Difference in LS means (95% CI) [a,b]	-0.57 (-2.26, 1.13)	-1.44 (-3.27, 0.39)	
p-value (one-sided non-inferiority test at a margin of 4 letters) [a,b]	<0.0001	0.0031	

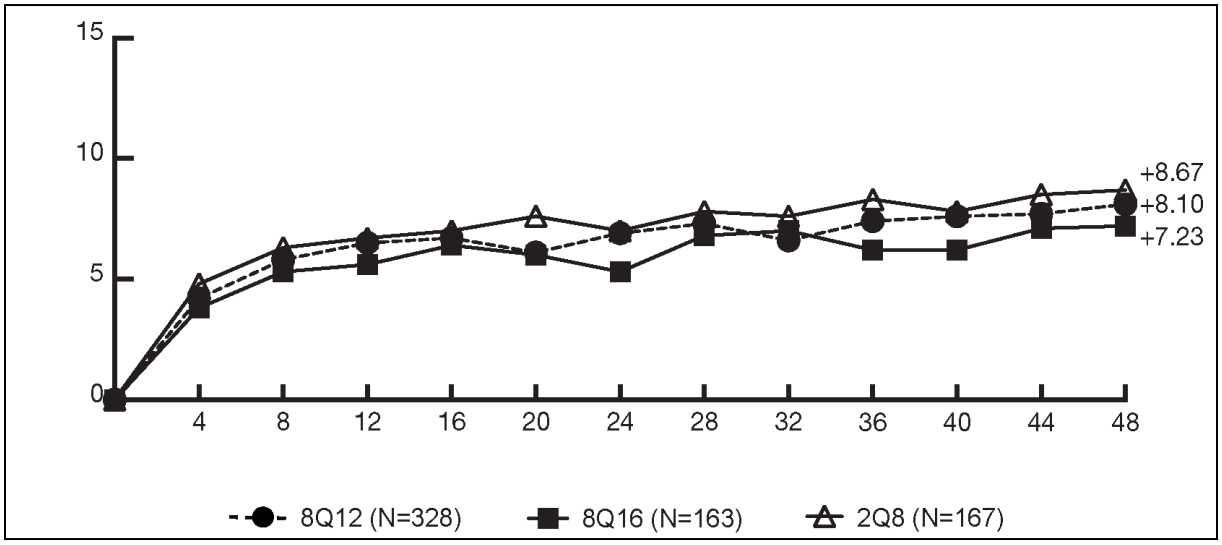
CI: Confidence interval; LS: Least square; SD: Standard deviation; SE: Standard error

a LS mean, CI and p-value based on an MMRM with baseline best corrected visual acuity (BCVA) measurement as covariate, treatment group as factor, visit and stratification variables used for randomisation (geographical region, categorical baseline BCVA) as fixed factors as well as terms for the interaction between baseline BCVA and visit and for the interaction between treatment and visit.

b Absolute difference is Eylea HD 8Q12- or 8Q16-groups minus Eylea 2Q8-groups, respectively.

c Full analysis set

Figure 11: LS mean change in BCVA as measured by ETDRS letter score from baseline through week 48 (full analysis set) in the PHOTON study



At week 48, 91.0% of patients in the 8Q12 group were maintained with the 8Q12 treatment interval and 89.1% of patients in the 8Q16 group were maintained with the 8Q16 treatment intervals.

In the PHOTON study, exploratory subgroup analyses showed that: the difference in LS means (Eylea HDQ12 vs. Eylea 2q8) in change in BCVA from baseline at Week 48 in the subgroup of patients aged < 65 years (n = 185 and 92, respectively) was -2.57 letters (95% CI, -4.81, -0.33) as compared to 2.01 letters (95% CI, -0.40, 4.42) in the subgroup of patients aged ≥ 65 years (n = 143 and 75, respectively); and, the difference in LS means (Eylea HDQ16 vs. Eylea 2q8) in change in BCVA from baseline at Week 48 in the subgroup of patients aged < 65 years (n = 92 and 92, respectively) was -2.71 letters (95% CI, -5.05, -0.37) as compared to 0.32 letters (95% CI, -2.38, 3.01) in the subgroup of patients aged ≥ 65 years (n = 71 and 75, respectively).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: The toxicological profile of aflibercept was assessed in several non-clinical repeated dose studies in monkeys. In brief, the following pivotal studies were performed:

1) a 9-week or 6-month repeat-dose intravitreal study with 12 weeks of recovery, where monkeys were administered aflibercept doses of 0, 4, or 7 mg/eye bilaterally every 4 weeks; the clinically relevant formulation for aflibercept 8 mg was used in the 6-month treatment arm. Erosions and ulcerations of the respiratory epithelium in nasal turbinates were observed in monkeys treated with aflibercept at all doses. A No Observed Adverse Effect Level (NOAEL) was not identified. At the Lowest Observed Adverse Effect Level (LOAEL) of 4 mg/eye in monkeys, the systemic exposure was 50- and 77-fold higher based on C_{max} and AUC when compared to corresponding values in wet AMD and DME patients after a unilateral intravitreal dose of 8 mg. Systemic toxicity was not fully assessed in this study.

2) an 8-month repeat-dose intravitreal study with 4-months of recovery, where monkeys were administered aflibercept bilaterally every 4 weeks at doses of 0, 0.5, 2, or 4 mg/eye in the marketed aflibercept 2 mg formulation. Systemic effects were limited to erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept at doses of 2 or 4 mg/eye. At the NOAEL of 0.5 mg/eye in monkeys, the systemic exposure was 3.2- and 3.8-fold higher based on C_{max} and AUC when compared to corresponding values in wet AMD and DME patients after a unilateral intravitreal dose of 8 mg.

3) a 6-month repeat-dose intravenous study with 5-months of recovery, where monkeys were administered aflibercept intravenously once weekly for 15 weeks; then once every 2 weeks for 12 weeks at doses of 0, 3, 10, or 30 mg/kg. No NOAEL was identified. At the Lowest Observed Adverse Effect Level (LOAEL) of 3 mg/eye in monkeys, the systemic exposure was 104-fold higher based on AUC when compared to corresponding values in wet AMD and DME patients after a unilateral intravitreal dose of 8 mg. Under these conditions and high systemic exposure, aflibercept can cause system-wide organ effects. Monkeys given aflibercept had reduced body weight and developed erosion/ulceration of the nasal turbinate epithelia leading to hemorrhage. Anemia related to bleeding as a result of lesions in the nasal cavity resulted in the premature euthanization of one monkey in the low-dose group. Monkeys administered doses ≥ 3 mg/kg developed deformity or abnormal bone growth of spinal vertebrae or bones of the limbs, along with muscular atrophy, and joint degeneration. Monkeys also developed renal inflammation and glomerulopathy accompanied by proteinuria and albuminuria. At doses ≥ 10 mg/kg, monkeys showed vascular degeneration/proliferation in tissues of the GI tract, heart, joints, and nervous system, as well as liver inflammation and necrosis.

Carcinogenicity: No studies have been conducted on the carcinogenic potential of aflibercept.

Genotoxicity: No studies have been conducted on the mutagenic potential of aflibercept.

Reproductive and Developmental Toxicology: Effects on male and female fertility were assessed as part of a 6-month repeat-dose intravenous study with 5-months of recovery, where monkeys were administered aflibercept intravenously once weekly for 15 weeks; then once every 2 weeks for 12 weeks at doses of 0, 3, 10, or 30 mg/kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. In addition, females showed decreased ovarian and uterine weight accompanied by compromised luteal development and reduction of maturing follicles. These changes correlated with uterine and vaginal atrophy. A NOAEL was not identified. Intravenous administration of the lowest dose

of aflibercept assessed in monkeys (3 mg/kg) resulted in systemic exposure (AUC) that was approximately 104-fold higher than the exposure in wet AMD and DME patients after a unilateral intravitreal dose of 8 mg. All changes were reversible within 20 weeks after cessation of treatment.

Aflibercept produced embryo-fetal toxicity in an embryo-fetal development study in pregnant rabbits with intravenous administration (3 to 60 mg/kg on gestation Days 6, 9, 12, 15 and 18). The maternal NOAEL was at the dose of 3 mg/kg. At this dose, the systemic exposures based on C_{max} and AUC for free aflibercept were approximately 226- and 46-fold higher than the exposure in wet AMD and DME patients after a unilateral intravitreal dose of 8 mg.

In embryo-fetal development studies in pregnant rabbits, aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg/kg (3 to 60 mg/kg on gestation day 6, 9, 12, 15, and 18), or every six days at subcutaneous doses ≥0.1 mg /kg (on gestation day 1, 7, and 13). Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal NOAEL in these studies was 3 mg per kg IV. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg SC. Administration of the lowest dose assessed in rabbits (0.1 mg per kg SC) resulted in systemic exposure (AUC) that was approximately 1.0 times the exposure in wet AMD and DME patients after a unilateral intravitreal dose of 8 mg.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrEYLEA® HD

Aflibercept injection, solution for intravitreal injection

Read this carefully before you start taking Eylea HD and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Eylea HD.

What is Eylea HD used for?

Eylea ("I-LEE-ah") HD is a solution which is injected into the eye (intravitreal injection) by your doctor with local anesthesia (freezing) to treat the eye conditions called:

- neovascular (wet) age-related macular degeneration – (wet) AMD,
- diabetic macular edema (DME).

How does Eylea HD work?

Growth factors (known as VEGF-A and PIGF) can cause extra blood vessels to grow and leak in the back of the eye, which can cause loss of vision.

Vascular Endothelial Growth Factor (VEGF) and Placental Growth Factor (PlGF) are proteins that play an important role in making the abnormal blood vessels that contribute to the progression of wet AMD and the macular edema (swelling) that is seen with diabetic macular edema (DME). These blood vessels are fragile and can leak fluid and blood into the macula, leading to vision loss. DME is a swelling of the retina occurring in patients with diabetes due to leaking of fluid from blood vessels within the macula. The macula is the portion of retina responsible for fine vision. When the macula swells with fluid, central vision becomes blurry.

Aflibercept, the active substance in Eylea HD, blocks these growth factors, and has been shown to help improve vision or slow vision loss from wet AMD and DME.

What are the ingredients in Eylea HD?

Medicinal ingredients: aflibercept

Non-medicinal ingredients: sucrose, L-arginine monohydrochloride, L-histidine monohydrochloride monohydrate, L-histidine, polysorbate 20, water for injection.

Eylea HD comes in the following dosage forms:

Eylea HD is a sterile, clear to slightly opalescent, colourless to pale yellow, solution for injection which is iso-osmotic (similar properties to the inside of your eye). Solution for intravitreal injection 8 mg / 0.07 mL in vial.

Each carton includes a single-dose glass vial containing a fill volume of 0.263 mL for Eylea HD solution for injection with a rubber stopper, and an 18 gauge filter needle.

Do not use Eylea HD if:

- you are allergic (hypersensitive) to aflibercept or any of the other ingredients of Eylea HD listed below or component of the container
- you have inflammation of the eye (symptoms include eye pain, redness and trouble seeing)
- you have an infection in or around the eye (ocular or periocular infection)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Eylea HD. Talk about any health conditions or problems you may have, including if you:

Take special care with Eylea HD:

- Injection with Eylea HD may trigger an increase in eye pressure (intraocular pressure) in some patients within 60 minutes of the injection. Your doctor may monitor this after each injection. If you have glaucoma (increased eye pressure), please tell your doctor.
- Although uncommon, all intravitreal injections, including those with Eylea HD, carry a risk of serious infection or inflammation inside the eye (endophthalmitis), detachment or tear of the retina at the back of the eye (symptoms include eye pain, worsening eye redness, blurred or decreased vision, sensitivity to light, sudden loss of vision, flashing lights and black spots), and cataracts (clouding of the lens in the front of the eye). **Please contact your doctor immediately if you develop any of these symptoms.**
- Inform your doctor if you have already had a stroke or experienced transient signs of stroke (weakness or paralysis of limbs or face, difficulty speaking or understanding). This information will be taken into account to evaluate if Eylea HD is the appropriate treatment for you.
- **Tell your doctor immediately if you develop signs of a possible allergic reaction** (for example, fast pulse, low blood pressure, sweating, allergic skin reactions such as rash, itching or stinging).

Before you use Eylea HD, talk to your doctor or pharmacist if:

- **You are taking other medicines:** Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
- **You are or plan to become pregnant:** There is no experience of using Eylea HD in pregnant women. In animals, high doses have been shown to have toxic effects on the fetus. Therefore, Eylea HD is not recommended during pregnancy. If you are pregnant or planning to become pregnant, discuss this with your doctor before treatment with Eylea HD. Women of childbearing potential have to use effective contraception during treatment and for at least 4 months after the last intravitreal injection of Eylea HD.
- **You are breast-feeding:** Eylea HD is not recommended during breast-feeding as it is not known whether aflibercept passes into human milk. A risk to the breast-fed child cannot be excluded. Ask your doctor for advice before starting Eylea HD treatment. A decision must be made whether to discontinue breast-feeding or to abstain from Eylea HD therapy.
- You have a history of seeing flashes of light or floaters, or if you have a sudden increase in the size or number of floaters.

The use of Eylea HD in children and adolescents has not been studied and is therefore not recommended.

Driving and Using Machines

After your Eylea HD injection, you may experience some temporary visual disturbances. Do not drive or use machinery as long as these last.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take Eylea HD:

Usual dose:

Eylea HD is intended for injection into the eye. It must only be administered by a doctor experienced in giving eye injections.

Eylea HD will be injected under aseptic (clean and sterile) conditions. Before the injection, your doctor will use a disinfectant eyewash to clean your eye carefully to prevent infection. Your doctor will also give you a local anesthetic to reduce or prevent any pain you might have with the injection.

Treatment of wet AMD

Eylea HD 8 mg (0.07 mL) will be administered once a month (every 4 weeks) for the first 3 months (12 weeks) then you may receive an injection every 2 months (8 weeks) or every 3 months (12 weeks) or every 4 months (16 weeks) thereafter. Your doctor will decide whether the treatment interval may need to be adjusted.

Treatment of DME

Eylea HD 8 mg (0.07 mL) will be administered once a month (every 4 weeks) for the first 3 months (12 weeks) then you may receive an injection every 2 months (8 weeks) or every 3 months (12 weeks) or every 4 months (16 weeks) thereafter. Your doctor will decide whether the treatment interval may need to be adjusted.

Use in children: The safety and efficacy of Eylea HD have not been studied in patients who are younger than 18 years of age. Health Canada has not authorized Eylea HD for pediatric use.

Before stopping Eylea HD treatment:

Consult your doctor before stopping the treatment. If you have any further questions about the use of this product, ask your doctor.

Overdose:

If you think you, or a person you are caring for, have taken too much Eylea HD, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If a dose of Eylea HD is missed, make a new appointment for an examination and injection as soon as possible.

What are possible side effects from using Eylea HD?

These are not all the possible side effects you may have when taking Eylea HD. If you experience any side effects not listed here, tell your healthcare professional.

Like all medicines, Eylea HD can cause side effects, although not everybody gets them.

With administration of Eylea HD, there may be some side effects due to the injection procedure. Some of these may be serious and include increase of pressure inside the eye (intraocular pressure) in AMD clinical studies for Eylea HD and intraocular pressure increase in DME clinical studies for Eylea HD.

These serious side effects occurred in 1 in 4,300 intravitreal injections with Eylea HD in the AMD study; and 1 in 1,500 intravitreal injections with Eylea HD in the DME study.

The following side effects of Eylea can also be expected with Eylea HD but have not been reported in the studies with Eylea HD:

- inflammation of certain parts of the eye (anterior chamber flare)
- damage of the front layer of the eyeball (corneal epithelium defect)
- certain forms of clouding of the lens (lenticular opacities)
- redness of the eye (ocular hyperemia)
- pus in front of the iris (coloured part of the eye) (hypopyon)
- clouding of the lens due to injury (cataract traumatic)
- severe allergies (severe anaphylactic/anaphylactoid reactions)

The following is a list of the side effects reported to be possibly related to the Eylea HD injection procedure or to the medicine. Please do not get alarmed, you might not experience any of these. Always discuss any suspected side effects with your doctor.

Common side effects (between 1 and 10 in every 100 patients may be affected):

- certain forms of clouding of the lens (cataract)
- bloodshot eye caused by bleeding from small blood vessels in the outer layers of the eye (conjunctival hemorrhage)
- moving spots in vision (vitreous floaters)
- detachment of the vitreous (gel-like substance inside the eye) from the retina (vitreous detachment)
- increase in eye pressure (intraocular pressure increased)
- eye pain
- damage to the front layer of the eyeball (punctate keratitis)

Uncommon side effects (between 1 and 10 in every 1,000 patients may be affected):

- generalized allergic reactions (hypersensitivity)*
- damage to the front layer of the eyeball (corneal abrasion, corneal erosion)
- decreased sharpness of vision (retinal pigment epithelium tear, detachment of the retinal pigment epithelium tear, retinal detachment, retinal tear)
- blurred vision
- pain or bleeding at the injection site (injection site pain or hemorrhage)
- certain forms of clouding of the lens (cataract subcapsular, cataract corticol, cataract nuclear)
- a feeling of having something in the eye (foreign body sensation in eyes)
- increased tear production (lacrimation increased)
- redness of the eye (conjunctival hyperemia)
- swelling of the eyelid (eyelid edema)
- inflammation of certain parts of the eye (iridocyclitis, vitritis, uveitis)
- inflammation in the iris of the eye (iritis)

* Allergic reactions like rash, itching (pruritus) and hives (urticaria) were reported.

The use of VEGF inhibitors similar to those contained in Eylea HD, but which have an effect throughout the body (systemic effect) is potentially related to risk of arterial thromboembolic events (ATEs) (of blood clots blocking blood vessels) which may lead to heart attack or stroke. There is a theoretical risk of such events following injection of Eylea HD into the eye.

As with all therapeutic proteins, Eylea HD may cause an immune reaction (formation of antibodies).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON (between 1 and 10 in every 100 patients may be affected)			
Clouding of vision (cataract)		✓	
Increased pressure in the eye		✓	
UNCOMMON (between 1 and 10 in every 1,000 patients may be affected)			
Visual disturbances caused by detachment of the inner layer of the eye (sudden loss of vision, flashing lights, black spots) (retinal detachment)		✓	
UNKNOWN			
Infection or inflammation inside the eye (endophthalmitis)		✓	
Shock (Hypersensitivity) – fast pulse, low blood pressure, sweating)		✓	
Signs of stroke, such as weakness or paralysis of limbs or face, trouble speaking or understanding, sudden blurring or loss of vision: seek emergency medical care immediately*		✓	
**There is a theoretical risk of ATEs, including stroke, following injection of Eylea HD into the eye.*			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep out of reach and sight of children.
- Store in a refrigerator (2°C to 8°C). Do not freeze.
- Prior to usage, the unopened Eylea HD vial may be stored at room temperature (25°C) for up to 24 hours.
- Keep the vial in its outer carton in order to protect from light.

If you want more information about Eylea HD:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website http://www.bayer.ca, or by calling Bayer Medical Information at 1-800-265-7382 or canada.medinfo@bayer.com.

This leaflet was prepared by:

Bayer Inc.
2920 Matheson Boulevard East
Mississauga, Ontario
L4W 5R6
Canada

Last Revised August 13, 2024