ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Eylea 114.3 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 114.3 mg aflibercept*.

Each vial contains 30.1 mg aflibercept in 0.263 ml solution. This provides a usable amount to deliver a single dose of 0.07 ml containing 8 mg aflibercept.

* Aflibercept is a fusion protein consisting of portions of human VEGF (vascular endothelial growth factor) receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)
Clear to slightly opalescent, colourless to pale yellow, iso-osmotic solution, pH 5.8.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Eylea is indicated in adults for the treatment of
- neovascular (wet) age-related macular degeneration (nAMD) (see section 5.1)
- visual impairment due to diabetic macular oedema (DME) (see section 5.1).

4.2 Posology and method of administration

Eylea must only be administered by a qualified physician experienced in intravitreal injections.

Posology

The recommended dose is 8 mg aflibercept, equivalent to 0.07 ml solution. The posology is the same for the nAMD and DME indications. The 8 mg dose requires use of the Eylea 114.3 mg/ml vial.

Eylea treatment is initiated with 1 injection per month for 3 consecutive doses. Injection intervals may then be extended up to every 4 months based on the physician's judgement of visual and/or anatomic outcomes. Subsequently, the treatment intervals may be further extended up to 5 months, such as with a treat-and-extend dosing regimen, while maintaining stable visual and/or anatomic outcomes (see section 5.1).

If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly based on the physician's discretion. The shortest interval between 2 injections is 2 months in the maintenance phase.

Eylea at monthly doses of 8 mg has not been studied for more than 3 consecutive doses.

The frequency of monitoring visits should be based on the patient's status and at the physician's discretion. For events in which treatment should be withheld see section 4.4.

Special populations

Renal or hepatic impairment
No specific studies in patients with renal or hepatic impairment have been conducted. Available data do not suggest a need for a dose adjustment with Eylea in these patients (see section 5.2).

Elderly
Available data do not suggest a need for a dose adjustment with Eylea in these patients.

Paediatric population
The safety and efficacy of Eylea 114.3 mg/ml in children and adolescents below 18 years have not been established. There is no relevant use of Eylea 114.3 mg/ml in the paediatric population in the nAMD and DME indications.

Method of administration

Eylea is for intravitreal injection only.

Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. In general, adequate anaesthesia and asepsis, including topical broad spectrum microbicide (e.g. povidone iodine applied to the periocular skin, eyelid and ocular surface), have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended.

The injection needle should be inserted 3.5 to 4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.07 ml is then delivered. A different scleral site should be used for subsequent injections.

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 (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Each vial should only be used for the treatment of a single eye.
After injection, discard any unused product or waste material in accordance with local requirements.

For handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Ocular or periocular infection.
- Active severe intraocular inflammation.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Intravitreal injection-related reactions

Intravitreal injections, including those with Eylea, have been associated with endophthalmitis, intraocular inflammation, retinal detachment, retinal tear and traumatic cataract (see section 4.8). Proper aseptic injection techniques must always be used when administering Eylea. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay and should be managed appropriately.

Intraocular pressure increased

Transient increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection, including those with Eylea (see section 4.8). Both the intraocular pressure and perfusion of the optic nerve head must therefore be monitored and managed appropriately. Special precaution is needed in patients with poorly controlled glaucoma (do not inject Eylea while the intraocular pressure is ≥ 30 mmHg).

Immunogenicity

As this is a therapeutic protein, there is a potential for immunogenicity with aflibercept (see section 5.1). Patients should be instructed to report any signs or symptoms of intraocular inflammation, e.g. pain, photophobia, or redness, which may be a clinical sign attributable to hypersensitivity.

Systemic effects

Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition (see section 4.8).
There are limited data on safety in the treatment of patients with nAMD and DME with a history of stroke, transient ischaemic attacks or myocardial infarction within the last 6 months. Caution should be exercised when treating such patients.

Bilateral treatment

The safety and efficacy of bilateral treatment with Eylea 114.3 mg/ml per eye have not been studied (see section 5.1). 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.

Concomitant use of other anti-VEGF

There are limited data available on the concomitant use of Eylea with other anti-VEGF medicinal products (systemic or ocular).

Withholding treatment

Treatment should be withheld in the event of:
- a decrease in best corrected visual acuity (BCVA) of ≥ 30 letters compared with the last assessment of visual acuity
- a rhegmatogenous retinal detachment or stage 3 or 4 macular holes
- a retinal break
- a subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥ 50 % of the total lesion area
- performed or planned intraocular surgery within the previous or next 28 days.

Retinal pigment epithelial tear

Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for nAMD include a large and/or high pigment epithelial retinal detachment. When initiating aflibercept therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.

Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment and for at least 4 months after the last intravitreal injection with Eylea 114.3 mg/ml (See section 4.6).

Populations with limited data

There is only limited experience with Eylea treatment in diabetic patients with an HbA1c over 12 % or with proliferative diabetic retinopathy.
Eylea 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 in diabetic patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment and for at least 4 months after the last intravitreal injection with Eylea 114.3 mg/ml.

Pregnancy

There are limited data on the use of aflibercept in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3).
Eylea 114.3 mg/ml should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.

Breast-feeding

Based on very limited human data, aflibercept may be excreted in human milk at low levels.
Aflibercept is a large protein molecule and the amount of medication absorbed by the infant is expected to be minimal. The effect of aflibercept on a breast-fed newborn/infant is unknown.
As a precautionary measure breast-feeding is not recommended during the use of Eylea 114.3 mg/ml.

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 section 5.3).

4.7 Effects on ability to drive and use machines

Injection with Eylea has minor influence on the ability to drive and use machines due to possible temporary visual disturbance associated either with the injection or eye examination. Patients should not drive or use machines until their visual function has recovered sufficiently.

4.8 Undesirable effects

Summary of the safety profile

Serious adverse reactions were cataract (4.0%), retinal haemorrhage (2.6%), intraocular pressure increased (2.4%), vitreous haemorrhage (1.0%), cataract subcapsular (0.5%), retinal detachment (0.4%), and retinal tear (0.3%).

The most frequently observed adverse reactions in patients treated with Eylea 114.3 mg/ml were cataract (4.0%), vitreous floaters (3.5%), visual acuity reduced (3.2%), conjunctival haemorrhage (3.1%), vitreous detachment (2.9%), retinal haemorrhage (2.6%), and intraocular pressure increased (2.4%).

The safety profile observed in the 3 clinical studies was similar in patients treated with Eylea 114.3 mg/ml (N=1 217) and Eylea 40 mg/ml (N=556), and in patients with nAMD and DME.

Tabulated list of adverse reactions

A total of 1 217 patients treated with Eylea 114.3 mg/ml constituted the safety population in 3 clinical phase II/III studies (CANDELA, PULSAR, PHOTON).
The safety data described below include all adverse reactions with a reasonable possibility of causality to the injection procedure or medicinal product reported .

The adverse reactions are listed by system organ class and frequency using the following convention: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: All treatment-emergent adverse reactions reported in patients with nAMD or DME treated with Eylea 114.3 mg/ml in phase II/III studies

System organ class	Common	Uncommon	Rare
Immune system disorders		Hypersensitivity*	
Eye disorders	Cataract, Intraocular pressure increased, Vitreous floaters, Vitreous detachment, Vitreous haemorrhage, Retinal haemorrhage, Visual acuity reduced, Eye pain, Conjunctival haemorrhage, Punctate keratitis	Retinal detachment, Retinal tear, Retinal pigment epithelial tear, Detachment of the retinal pigment epithelium, Iritis, Iridocyclitis, Vitritis, Cataract cortical, Cataract nuclear, Cataract subcapsular, Corneal erosion, Corneal abrasion, Vision blurred, Injection site pain, Foreign body sensation in eyes, Lacrimation increased, Injection site haemorrhage, Conjunctival hyperaemia	Blindness, Uveitis, Eyelid oedema, Injection site irritation, Corneal oedema

* Reports of hypersensitivity included rash, pruritus, urticaria.

The following adverse reactions of Eylea 40 mg/ml are also considered expected with Eylea 114.3 mg/ml but have not been reported in the clinical studies with Eylea 114.3 mg/ml: ocular hyperaemia, retinal degeneration, abnormal sensation in eye, lenticular opacities, corneal epithelium defect, anterior chamber flare, eyelid irritation, endophthalmitis, traumatic cataract, hypopyon, severe anaphylactic/anaphylactoid reactions.

Description of selected adverse reactions

Product-class-related adverse reactions
Arterial thromboembolic events (ATEs) are adverse reactions potentially related to systemic VEGF inhibition. There is a theoretical risk of ATEs, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors. A low incidence rate of ATEs was observed in the aflibercept clinical studies in patients with nAMD and DME. Across indications, no notable difference between the groups treated with Eylea 114.3 mg/ml and the comparator groups treated with Eylea 40 mg/ml were observed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

To report any side effect(s):
The National Pharmacovigilance Centre (NPC).
SFDA call center: 19999.
E - mail: npc.drug@sfda.gov.sa.
Website: https://ade.sfda.gov.sa

4.9 Overdose

Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdose, intraocular pressure should be monitored and, if deemed necessary by the treating physician, adequate treatment should be initiated (see sections 4.4 and 6.6).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals / Antineovascularisation agents, ATC code: S01LA05

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1.

Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.

Mechanism of action

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two 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 leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF can act independently to activate the VEGFR-1 to promote an inflammatory response within the retina, and is known to increase in pathological states such as nAMD, diabetic retinopathy (DR), DME, and retinal vein occlusion (RVO).

Pharmacodynamic effects

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.
In animal studies, aflibercept can prevent pathological neovascularization and vascular leakage in a number of different models of ocular disease.

nAMD

nAMD is characterised by pathological choroidal neovascularisation (CNV). Leakage of blood and fluid from CNV may cause retinal oedema and/or sub-/intra-retinal haemorrhage, resulting in loss of visual acuity.

The pharmacodynamic effects of aflibercept 114.3 mg/ml administered every 12 (8Q12) and every 16 (8Q16) weeks are described in comparison with aflibercept 40 mg/ml administered every 8 weeks (2Q8) for the nAMD indication. These effects are shown as the change in CNV size from baseline to week 12; change in total lesion area from baseline to weeks 48 and 60; and change from baseline in central retinal thickness (CRT).

In the pooled group of patients treated with 8Q12 or 8Q16, reductions in CNV size (LS mean, based on a mixed model for repeated measurements [MMRM]) at week 12 were -1.63 mm^2 compared to -1.17 mm^2 for patients treated with 2Q8.

Table 2: Pharmacodynamic parameter (full analysis set) in the PULSAR study

Efficacy outcomes	Week	Eylea 8Q12 (N = 335)	Eylea 8Q16 (N = 338)	Eylea 2Q8 (N = 336)
Change in total lesion area from baseline [mm^2]				
LS mean [A]	12	-0.55		-0.30
Arithmetic mean (SD), observed	48	-0.4 (2.9)	-0.2 (3.1)	0.1 (3.6)
LS mean (SE) [A]		-0.46 (0.19)	-0.35 (0.20)	0.09 (0.22)
Difference in LS means (95% CI) [A,B]		-0.55 (-1.04, -0.06)	-0.44 (-0.94, -0.06)	
Arithmetic mean (SD), observed	60	-0.5 (2.8)	-0.4 (3.2)	-0.3 (3.2)
LS mean (SE) [A]		-0.48 (0.20)	-0.54 (0.21)	-0.24 (0.20)
Difference in LS means (95% CI) [A,B]		-0.24 (-0.72, 0.24)	-0.29 (-0.79, 0.20)	

[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 8Q12- or 8Q16-groups minus 2Q8-groups, respectively.

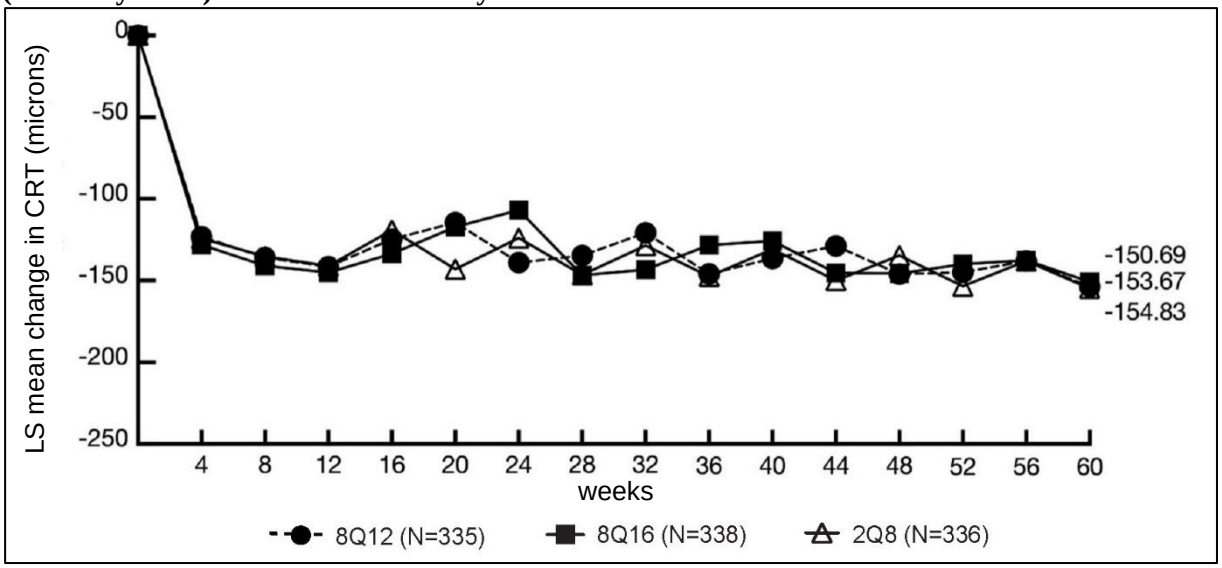
CI: Confidence interval

LS: Least square

SD: Standard deviation

SE: Standard error

Figure 1: LS mean change in central retinal thickness (CRT) from baseline through week 60 (full analysis set) in the PULSAR study



DME

Diabetic macular oedema is characterised by increased vasopermeability and damage to the retinal capillaries which may result in loss of visual acuity.

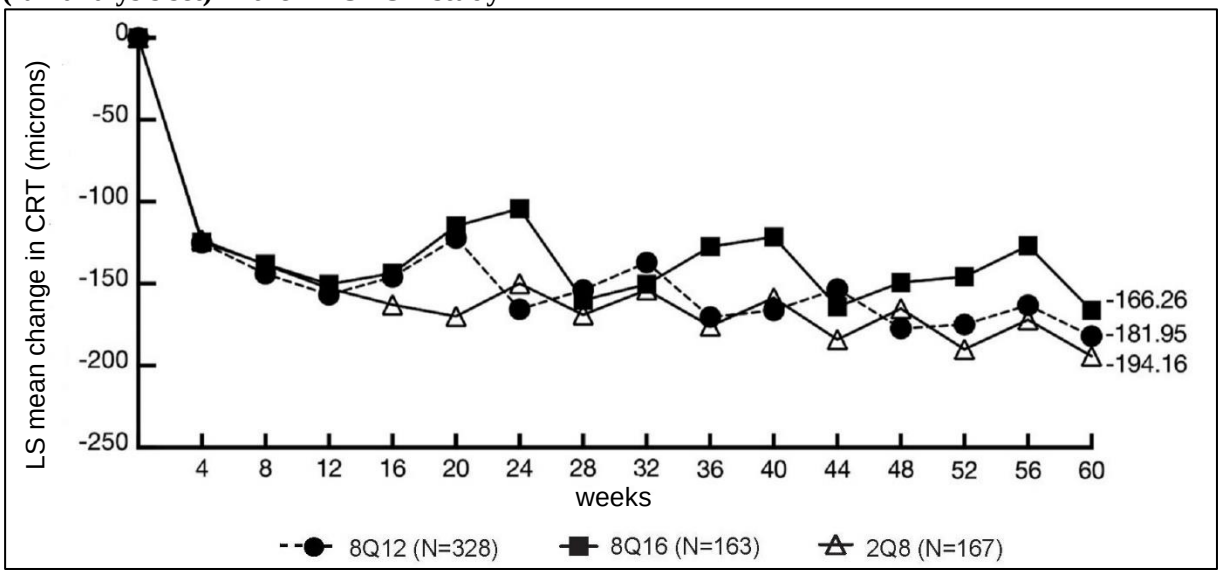
The pharmacodynamic effects of aflibercept 114.3 mg/ml administered every 12 (8Q12) and every 16 (8Q16) weeks are described in comparison with aflibercept 40 mg/ml administered every 8 weeks (2Q8) for the DME indication. These effects are shown as the change in the leakage area from baseline to weeks 48 and 60.

Table 3: Pharmacodynamic parameter (full analysis set) in the PHOTON study

Efficacy Outcomes	Week	Eylea 8Q12 (N = 328)	Eylea 8Q16 (N = 163)	Eylea 2Q8 (N = 167)
Change in leakage area from baseline [mm^2]				
Arithmetic mean (SD), observed	48	-13.9 (13.91)	-9.4 (11.50)	-9.2 (12.11)
	60	-13.9 (13.54)	-12.0 (13.26)	-14.4 (12.89)

SD: Standard deviation

Figure 2: LS mean change in central retinal thickness (CRT) from baseline through week 60 (full analysis set) in the PHOTON study



Immunogenicity
After dosing with Eylea 114.3 mg/ml for up to 48 weeks treatment-emergent antibodies to Eylea 114.3 mg/ml were detected in 1.2% to 3.8% of patients treated for DME and nAMD. No evidence of anti-drug antibodies impact on pharmacokinetics, efficacy or safety was observed.

Clinical efficacy and safety

nAMD

Study objectives
The safety and efficacy of Eylea 114.3 mg/ml were assessed in a randomised, multi-centre, double-masked, active-controlled study (PULSAR) in patients with treatment naïve nAMD.

The primary objective was to determine if treatment with Eylea 114.3 mg/ml at intervals of 12 (8Q12) or 16 weeks (8Q16) provides non-inferior best corrected visual acuity (BCVA) change compared to Eylea 40 mg/ml every 8 weeks in patients with nAMD.
The secondary objectives were to determine the effect of Eylea 114.3 mg/ml versus Eylea 40 mg/ml on anatomic and other visual measures of response, and to evaluate the safety, immunogenicity, and pharmacokinetics of aflibercept.

The primary efficacy endpoint was the change from baseline in BCVA measured by the early treatment diabetic retinopathy study (ETDRS) letter score at week 48.
The key secondary endpoints were the change in BCVA from baseline at week 60 and the proportion of patients with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in central subfield at week 16. Further secondary endpoints were the proportion of patients gaining at least 15 letters in BCVA from baseline at week 48, the proportion of patients achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at week 48, and the change from baseline in National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) total score at week 48, among others.

In the PULSAR study a total of 1 009 patients were treated. The patients were assigned in a 1:1:1 ratio to 1 of 3 parallel treatment groups:
1. Eylea 114.3 mg/ml administered every 12 weeks (8Q12)
2. Eylea 114.3 mg/ml administered every 16 weeks (8Q16)
3. Eylea 40 mg/ml administered every 8 weeks (2Q8)

All patients received 3 initial injections of the assigned dose at 4-week intervals.
Per study protocol the interval of the 8Q12- and 8Q16-groups was to be shortened if both of the following criteria were met:
1. >5 letters loss in BCVA from week 12, and
2. >25 microns increase in CRT from week 12 or new foveal haemorrhage or new foveal neovascularisation.

Regardless of whether patient intervals were maintained or shortened in year 1, per study protocol all patients in the 8Q12- and 8Q16-groups were eligible for interval extension (by 4 weeks increments), beginning at week 52, if the following criteria were met:
1. <5 letters loss in BCVA from week 12, and
2. no fluid in the central subfield on optical coherence tomography (OCT), and
3. no new onset of foveal haemorrhage or foveal neovascularisation.

For patients who did not meet the criteria for shortening or extension of the interval, the dosing interval was maintained. The minimum interval between injections was 8 weeks in all groups.
Patients with bilateral disease were eligible to receive Eylea 40 mg/ml treatment or another anti-VEGF medicinal product in their fellow eye.

Patient characteristics at baseline
Patient ages ranged from 50 to 96 years with a mean of 74.5 years.
Approximately 92% (309/335) and 87% (295/338) of the patients randomised to the 8Q12- and 8Q16-groups, respectively, were 65 years of age or older and approximately 51% (172/335) and 51% (171/338) were 75 years of age or older.

Results
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.
At week 48, in the 8Q12-group, 79.4% of patients maintained Q12 intervals while in the 8Q16-group 76.6% of patients maintained Q16 intervals.
Patients in the 8Q12-, 8Q16- and 2Q8-groups who completed week 60 received a median (mean) of 7.0 (7.1), 6.0 (6.2) and 9.0 (8.8) injections, respectively.
At week 60, 43.1% of patients in the 8Q12-group were extended to a dosing interval of 16 weeks, and 38.5% of patients in the 8Q16-group were extended to a dosing interval of 20 weeks.

Treatment with 8Q12 and 8Q16 was shown to be non-inferior and clinically equivalent to treatment with 2Q8 in terms of the primary efficacy endpoint ‘mean change in BCVA at week 48’ and the key secondary efficacy endpoint ‘mean change in BCVA at week 60’.

Furthermore, treatment with Eylea (pooled 8Q12- and 8Q16-groups) was shown to be superior to treatment with 2Q8 in terms of the key secondary efficacy endpoint ‘proportion of patients with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in the central subfield at week 16’ (see table 4).

Table 4: Efficacy outcomes from the PULSAR study

Efficacy outcomes	Week	Eylea 8Q12 (N = 335)	Eylea 8Q16 (N = 338)	Eylea 2Q8 (N = 336)
Change in BCVA from baseline as measured by ETDRS letter score [D]				
Arithmetic mean (SD), observed	48	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 (95% CI) [A,B]		-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	
Arithmetic mean (SD), observed	60	6.6 (13.6)	6.6 (11.7)	7.8 (12.6)
LS mean (SE) [A]		6.37 (0.74)	6.31 (0.66)	7.23 (0.68)
Difference in LS means (95% CI) [A,B]		-0.86 (-2.57, 0.84)	-0.92 (-2.51, 0.66)	
p-value (one-sided non-inferiority test at a margin of 4 letters) [A,B]		0.0002	<0.0001	
Patients with no IRF and no SRF in the central subfield [D]				
Proportion (LOCF)	16	63.3%		51.6%
Adjusted difference in proportion (95% CI) [B,C]		11.7% (5.3%, 18.2%)		
p-value (one-sided superiority test) [B, C]		0.0002		
Proportion (LOCF)	48	71.1%	66.8%	59.4%
Adjusted difference in proportion (95% CI) [B,C]		11.7% (4.5%, 18.9%)	7.5% (0.1%, 14.8%)	
Proportion (LOCF)	60	74.6%	72.2%	74.6%
Adjusted difference in proportion (95% CI) [B,C]		0.0% (-6.6%, 6.7%)	-2.2% (-8.9%, 4.4%)	
Patients achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) [D]				
Proportion (LOCF)	48	56.9%	54.3%	57.9%
Adjusted difference in proportion (95% CI) [B,C]		-0.2% (-6.6%, 6.2%)	-2.2% (-8.4%, 4.0%)	
Proportion (LOCF)	60	56.3%	54.6%	58.2%
Adjusted difference in proportion (95% CI) [B,C]		-1.1% (-7.5%, 5.3%)	-2.3% (-8.7%, 4.1%)	
Patients who gained at least 15 letters in BCVA from baseline [D]				
Proportion (LOCF)	48	20.7%	21.7%	22.1%
Adjusted difference in proportion (95% CI) [B,C]		-1.7% (-7.8%, 4.3%)	-0.9% (-7.0%, 5.1%)	
Proportion (LOCF)	60	23.7%	23.1%	23.3%
Adjusted difference in proportion (95% CI) [B,C]		0.1% (-6.2%, 6.3%)	-0.7% (-6.9%, 5.5%)	

[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 8Q12- or 8Q16-groups minus 2Q8-groups, respectively.

[C] Mantel-Haenszel weighted treatment difference with stratification variables used for randomization (geographical region, categorical baseline BCVA) and CI calculated using normal approximation.

[D] Full analysis set

CI: Confidence interval

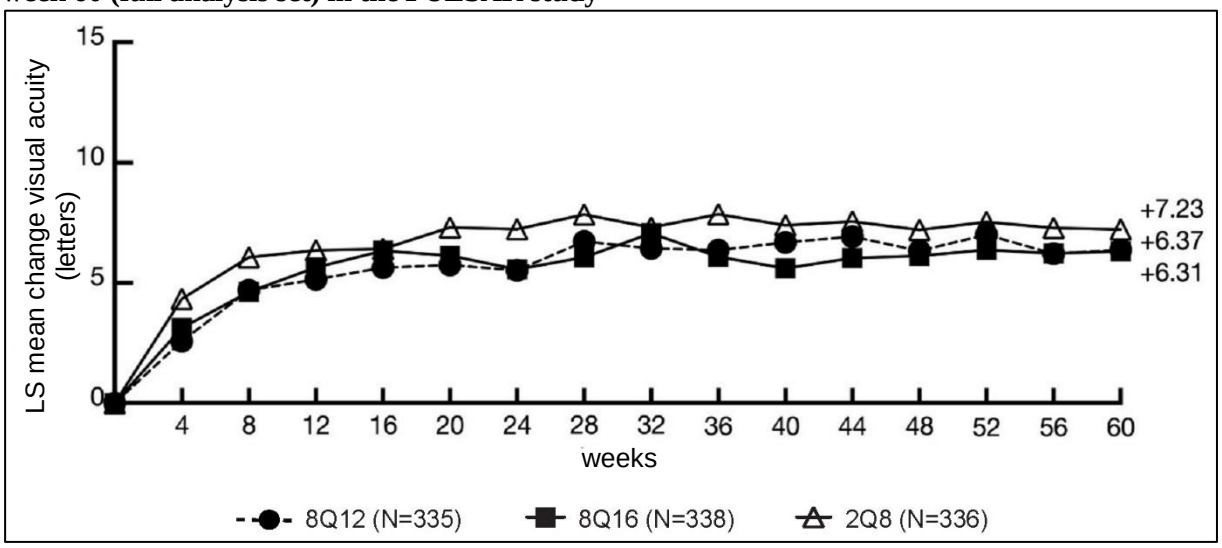
LOCF: Last observation carried forward

LS: Least square

SD: Standard deviation

SE: Standard error

Figure 3: LS mean change in BCVA as measured by ETDRS letter score from baseline through week 60 (full analysis set) in the PULSAR study



Aflibercept at all doses (8Q12, 8Q16, 2Q8) demonstrated meaningful increase from baseline in the pre-specified secondary efficacy endpoint national eye institute visual function questionnaire (NEI VFQ-25).
No clinically meaningful differences were found between the 8Q12-, 8Q16- and 2Q8-groups in changes of NEI VFQ-25 total score at week 48 from baseline.

Efficacy results in evaluable subgroups for age, gender, geographic region, ethnicity, race, baseline BCVA, and lesion type were consistent with the results in the overall population.
Efficacy was generally maintained through week 60.

DME

Study objectives
The safety and efficacy of Eylea 114.3 mg/ml were assessed in a randomised, multi-centre, double-masked, active-controlled study (PHOTON) in patients with DME.

The primary objective was to determine if treatment with Eylea 114.3 mg/ml at intervals of 12 or 16 weeks provides non-inferior BCVA change compared to Eylea 40 mg/ml every 8 weeks.
The secondary objectives were to determine the effect of Eylea 114.3 mg/ml versus Eylea 40 mg/ml on anatomic and other visual measures of response, and to evaluate the safety, immunogenicity, and pharmacokinetics of aflibercept.

The primary efficacy endpoint was the change from baseline in BCVA measured by the early treatment diabetic retinopathy study (ETDRS) letter score at week 48.
One key secondary endpoint was the change in BCVA from baseline at week 60.
Further secondary endpoints were the proportion of patients gaining at least 15 letters in BCVA from baseline at week 48, the proportion of patients achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at week 48, and the change from baseline in National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) total score at week 48, among others.

In the PHOTON study a total of 658 patients were treated. The patients were assigned in a 2:1:1 ratio to 1 of 3 parallel treatment groups:
1. Eylea 114.3 mg/ml administered every 12 weeks (8Q12)
2. Eylea 114.3 mg/ml administered every 16 weeks (8Q16)
3. Eylea 40 mg/ml administered every 8 weeks (2Q8)

All patients in the 8Q12- and 8Q16-groups received 3 initial injections and all patients in the 2Q8-group received 5 initial injections at 4-week intervals.

Per study protocol the interval of the 8Q12- and 8Q19-groups was to be shortened if both of the following criteria were met:
1. >10 letter loss in BCVA from week 12 in association with persistent or worsening DME, and
2. >50 microns increase in CRT from week 12.

Regardless of whether patient intervals were maintained or shortened in year 1, per study protocol all patients in the 8Q12- and 8Q16-groups were eligible for interval extension (by 4 weeks increments), beginning at week 52, if the following criteria were met:
1. <5 letter loss in BCVA from week 12, and
2. CRT <300 microns on SD-OCT (or <320 microns if measured including RPE).

For patients who did not meet the criteria for shortening or extension of the interval, the dosing interval was maintained. The minimum interval between injections was 8 weeks in all groups. Patients with bilateral disease were eligible to receive Eylea 40 mg/ml treatment in their fellow eye.

Patient characteristics at baseline
Patient ages ranged from 24 to 90 years with a mean of 62.3 years.
Approximately 44% (143/328) and 44% (71/163) of the patients randomised to the 8Q12- and 8Q16-groups, respectively, were 65 years of age or older and approximately 11% (36/328) and 14% (14/163) were 75 years of age or older.
The proportion of patients who were treated previously for DME was balanced between the treatment groups (43.6% in 8Q12-, 43.6% in 8Q16-, 44.3% in 2Q8-group).

Results
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.
At week 48, in the 8Q12-group, 91.0% of patients maintained Q12 intervals while in the 8Q16-group 89.1% of patients maintained Q16 intervals.
Patients in the 8Q12-, 8Q16- and 2Q8-groups who completed week 60 received a median (mean) of 7.0 (7.0), 6.0 (6.0) and 10.0 (9.8) injections, respectively. At week 60, 42.6% of patients in the 8Q12-group were extended to a dosing interval of 16 weeks, and 34.2% of patients in the 8Q16-group were extended to a dosing interval of 20 weeks.

Treatment with Eylea (both 8Q12- and 8Q16-groups) was shown to be non-inferior and clinically equivalent to treatment with 2Q8 in terms of the primary efficacy endpoint ‘mean change in BCVA at week 48’ and the key secondary efficacy endpoint ‘mean change in BCVA at week 60’.

Table 5: Efficacy outcomes from the PHOTON study

Efficacy outcomes	Week	Eylea 8Q12 (N = 328)	Eylea 8Q16 (N = 163)	Eylea 2Q8 (N = 167)
Change in BCVA from baseline as measured by ETDRS letter score [D]				
Arithmetic mean (SD), observed	48	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	
Arithmetic mean (SD), observed	60	9.05 (9.27)	7.96 (9.14)	9.62 (9.58)
LS mean (SE) [A]		8.52 (0.63)	7.64 (0.75)	9.40 (0.77)
Difference in LS means (95% CI) [A,B]		-0.88 (-2.67, 0.91)	-1.76 (-3.71, 0.19)	
p-value (one-sided non-inferiority test at a margin of 4 letters) [A,B]		0.0003	0.0122	
Patients achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) [D]				
Proportion (LOCF)	48	65.3%	62.6%	63.0%
Adjusted difference in proportion (95% CI) [B,C]		2.45% (-6.47%, 11.36%)	-0.67% (-11.16%, 9.82%)	
Proportion (LOCF)	60	64.7%	62.0%	60.6%
Adjusted difference in proportion (95% CI) [B,C]		4.34% (-4.72%, 13.40%)	1.63% (-8.91%, 12.17%)	
Patients who gained at least 15 letters in BCVA from baseline [D]				
Proportion (LOCF)	48	18.7%	16.6%	23.0%
Adjusted difference in proportion (95% CI) [B,C]		-4.64% (-12.30%, 3.02%)	-7.14% (-15.45%, 1.17%)	
Proportion (LOCF)	60	21.5%	16.0%	26.1%
Adjusted difference in proportion (95% CI) [B,C]		-5.01% (-13.04%, 3.02%)	-10.78% (-19.27%, -2.29%)	

[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 8Q12- or 8Q16-groups minus 2Q8-groups, respectively.

[C] Mantel-Haenszel weighted treatment difference with stratification variables used for randomization (geographical region, categorical baseline BCVA) and CI calculated using normal approximation.

[D] Full analysis set

CI: Confidence interval

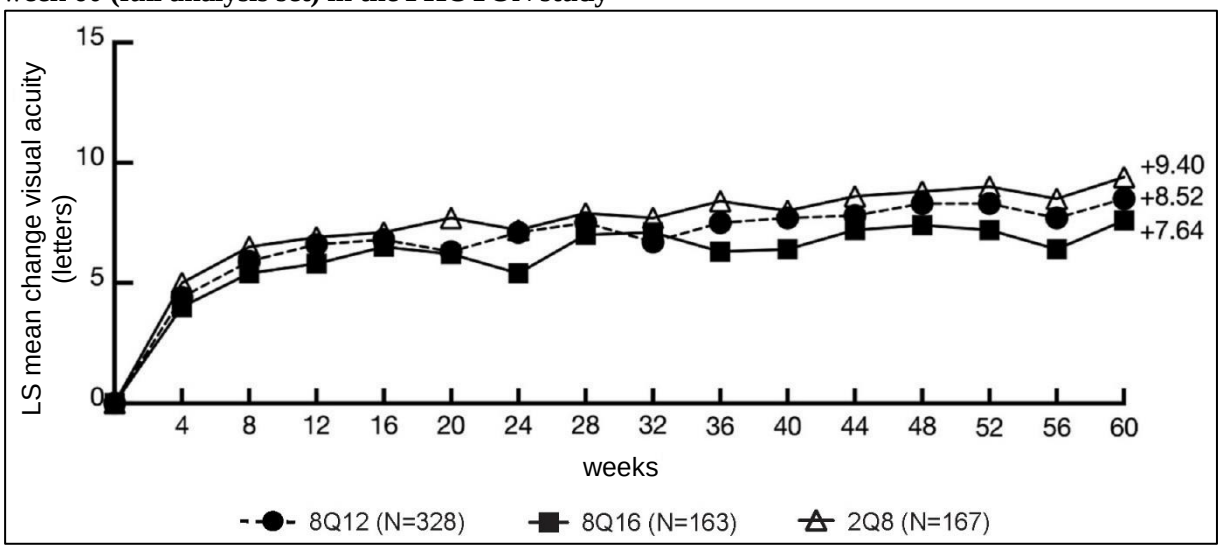
LOCF: Last observation carried forward

LS: Least square

SD: Standard deviation

SE: Standard error

Figure 4: LS mean change in BCVA as measured by ETDRS letter score from baseline through week 60 (full analysis set) in the PHOTON study



Eylea at all doses (8Q12, 8Q16, 2Q8) demonstrated meaningful increase from baseline in the pre-specified secondary efficacy endpoint national eye institute visual function questionnaire (NEI VFQ-25).
No clinically meaningful differences were found between the 8Q12-, 8Q16- and 2Q8-groups in changes of NEI VFQ-25 total score at week 48 from baseline.

Efficacy results in evaluable subgroups for age, gender, geographic region, ethnicity, race, baseline BCVA and baseline CRT and prior DME treatment were consistent with the results in the overall population.
Efficacy was generally maintained through week 60.

Treatment effects in the sub-group of previously treated patients were similar to those seen in patients who were treatment naïve.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with aflibercept in all subsets of the paediatric population in nAMD and DME (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption / Distribution

Aflibercept is slowly absorbed from the eye into the systemic circulation after intravitreal administration and is predominately observed in the systemic circulation as an inactive, stable complex with VEGF; however only “free aflibercept” is able to bind endogenous VEGF.

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 concentration in plasma was 1 day, in the nAMD and DME population combined. The accumulation of free aflibercept in plasma following 3 initial monthly doses was minimal. Subsequently, no further accumulation was observed. These data are also supported by population pharmacokinetic analyses.

Elimination

Aflibercept is a protein-based therapeutic and no metabolism studies have been conducted.

Aflibercept is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis. The median time to reach the last quantifiable concentration of free aflibercept in plasma for 8 mg administered intravitreally was 3 weeks.

Renal or hepatic impairment

No special studies in patients with renal or hepatic impairment have been conducted with Eylea 114.3 mg/ml.

The systemic exposures to aflibercept in patients with mild to severe renal impairment were similar to those with normal renal function. Limited available data in patients with mild hepatic impairment do not indicate an influence on systemic exposures to aflibercept compared to patients with normal hepatic function.

5.3 Preclinical safety data

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at systemic exposures in excess of the maximum human exposure. The systemic exposure for free aflibercept was approximately 26- and 33-fold higher based on C_{max} and AUC when compared to corresponding values in adult patients after an intravitreal dose of 8 mg. At the No Observed Adverse Effect Level (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 adult patients.

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept.

An effect of aflibercept on intrauterine development was shown in embryo-foetal development studies in pregnant rabbits with intravenous (3 to 60 mg/kg) as well as subcutaneous (0.1 to 1 mg/kg) administration. The maternal NOAEL was at the dose of 3 mg/kg or 1 mg/kg, respectively. A developmental NOAEL was not identified. At the 0.1 mg/kg dose, the systemic exposure for free aflibercept was approximately 1.0- and 1.0-fold based on C_{max} and cumulative AUC when compared to corresponding values in adult patients after an intravitreal dose of 8 mg.

Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at doses ranging from 3 to 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. Based on C_{max} and AUC for free aflibercept observed at the 3 mg/kg intravenous dose, the systemic exposures were approximately 377-fold and 104-fold higher, respectively, than the exposure in humans after an intravitreal dose of 8 mg. All changes were reversible.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Arginine hydrochloride
Histidine hydrochloride monohydrate
Histidine
Polysorbate 20
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Vial (type I glass) with a grey rubber stopper (chlorobutyl) sealed with an aluminium cap with white lid, and a 18 G, 5-micron filter needle.
Each vial contains 0.263 ml solution.
Pack size of 1 vial and 1 filter needle.

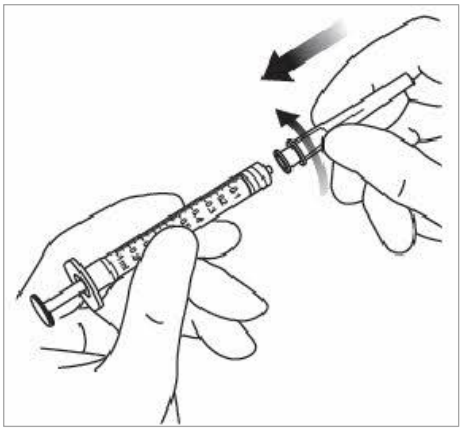
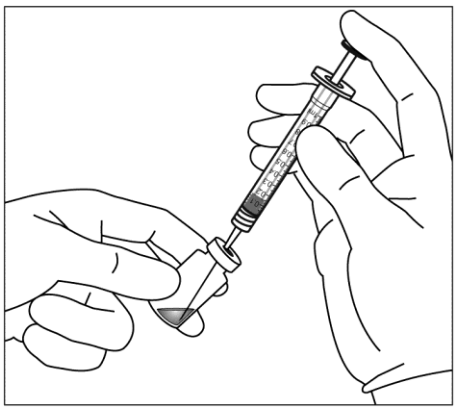
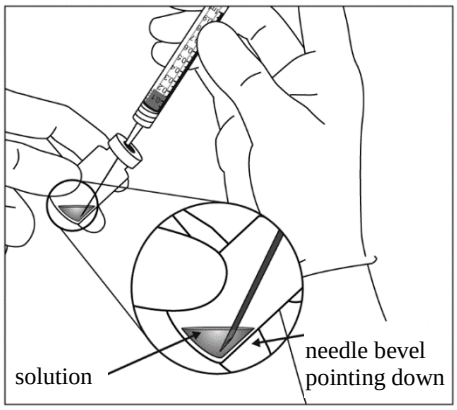
6.6 Special precautions for disposal and other handling

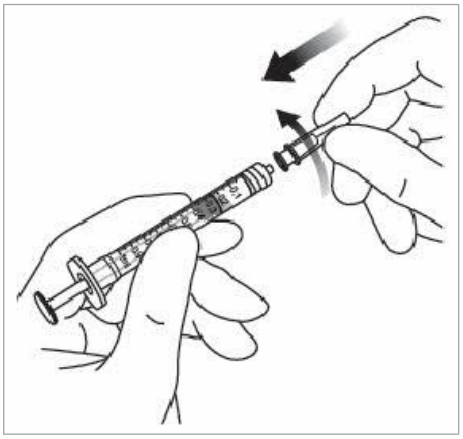
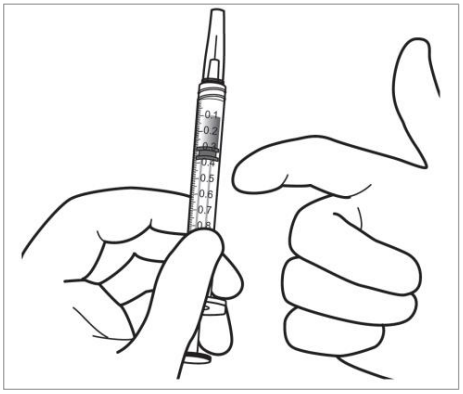
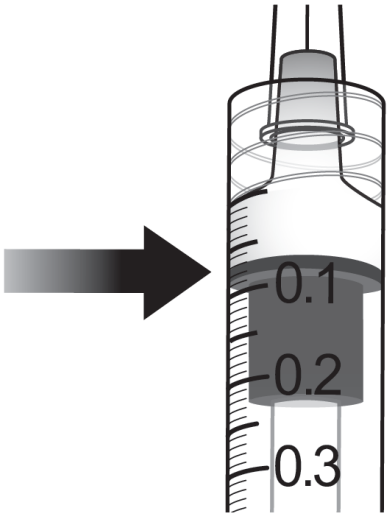
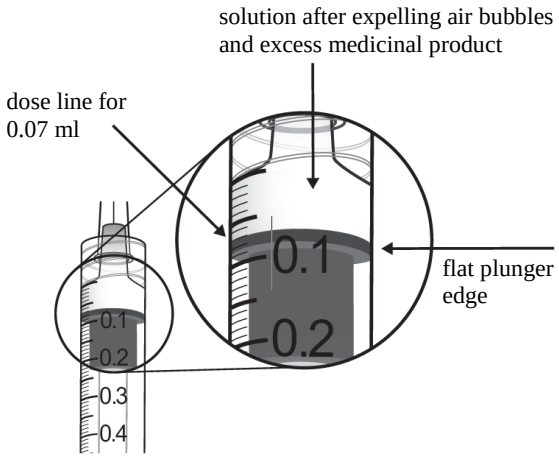
The vial is for single use in one eye only. Extraction of multiple doses from a single vial may increase the risk of contamination and subsequent infection.

Do not use if the package or its components are expired, damaged, or have been tampered with.
Check the label on the vial to make sure you have the strength of Eylea that you intended to use. The 8 mg dose requires use of the Eylea 114.3 mg/ml vial.

18 G, 5-micron filter needle:
- BD blunt filter (fill) needle, not for skin injection.
- Do not autoclave BD blunt filter (fill) needle.
- The filter needle is non-pyrogenic. Do not use it if individual packaging is damaged.
- Discard the used BD Blunt Filter (Fill) Needle in approved sharps collector.
- Caution: Re-use of the filter needle may lead to infection or other illness/injury.

The intravitreal injection should be performed with a 30 G × ½ inch injection needle (not included).

1.	Prior to administration visually inspect the solution for injection. Do not use the vial if particulates, cloudiness, or discolouration are visible.
2.	Remove the plastic cap and disinfect the outer part of the rubber stopper of the vial. 
3.	Use aseptic technique to carry out steps 3-10. Attach the filter needle supplied in the carton to a 1-ml sterile, Luer-lock syringe. 
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 or bottom edge of the vial.
5.	Withdraw all of the Eylea vial content 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.  
6.	Ensure that the plunger rod is drawn sufficiently back when emptying the vial to completely empty the filter needle. After injection any unused product must be discarded.
7.	Remove the filter needle and properly dispose of it. **Note:** The filter needle is **not** to be used for the intravitreal injection.

8.	Firmly twist the 30 G × ½ inch injection needle onto the Luer-lock syringe tip.	
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.	
10.	To eliminate all bubbles and to expel excess medicinal product, slowly depress the plunger so that the flat plunger edge aligns with the line that marks **0.07 ml** on the syringe.	
		

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/797/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2012
Date of latest renewal: 13 July 2017

10. DATE OF REVISION OF THE TEXT