1. NAME OF THE MEDICINAL PRODUCT

Eylea 114.3 mg/ml solution for injection
Eylea 114.3 mg/ml solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 114.3 mg aflibercept*.

Eylea 114.3 mg/ml solution for injection

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.

Eylea 114.3 mg/ml solution for injection in pre-filled syringe

Each pre-filled syringe contains 21 mg aflibercept in 0.184 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 Eylea 114.3 mg/ml.

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 or pre-filled syringe 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 Fertility, 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 (8.2%), retinal haemorrhage (3.6%), intraocular pressure increased (2.8%), vitreous haemorrhage (1.2%), cataract subcapsular (0.9%), cataract nuclear (0.6%), retinal detachment (0.6%), and retinal tear (0.5%).

The most frequently observed adverse reactions in patients treated with Eylea 114.3 mg/ml were cataract (8.2%), visual acuity reduced (4.4%), vitreous floaters (4.0%), conjunctival haemorrhage (3.8%), vitreous detachment (3.7%), retinal haemorrhage (3.6%), intraocular pressure increased (2.8%), and eye pain (2.0%).

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, Corneal abrasion	Retinal detachment, Retinal tear, Retinal pigment epithelial tear, Detachment of the retinal pigment epithelium, Uveitis, Iritis, Iridocyclitis, Vitritis, Cataract cortical, Cataract nuclear, Cataract subcapsular, Corneal erosion, Vision blurred, Injection site pain, Foreign body sensation in eyes, Lacrimation increased, Injection site haemorrhage, Conjunctival hyperaemia,	Corneal oedema, Lenticular opacities, Retinal degeneration, Eyelid irritation

		Eyelid oedema, Ocular hyperaemia, Injection site irritation	

* 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: abnormal sensation in eye, corneal epithelium defect, anterior chamber flare, endophthalmitis, blindness, 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

België
Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten – www.fagg.be
Afdeling Vigilantie
Website: www.eenbijwerkingmelden.be
e-mail: adr@fagg.be

Luxemburg
Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé
Site internet : www.guichet.lu/pharmacovigilance

Nederland
Nederlands Bijwerkingen Centrum Lareb
Website: www.lareb.nl

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, 60, and 96; 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)	
Arithmetic mean (SD), observed	96	-0.3 (3.3)	-0.3 (3.2)	-0.2 (3.4)
LS mean (SE) [A]		-0.43 (0.20)	-0.42 (0.20)	-0.18 (0.20)
Difference in LS means (95% CI) [A,B]		-0.25 (-0.72, 0.21)	-0.24 (-0.71, 0.22)	

[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.

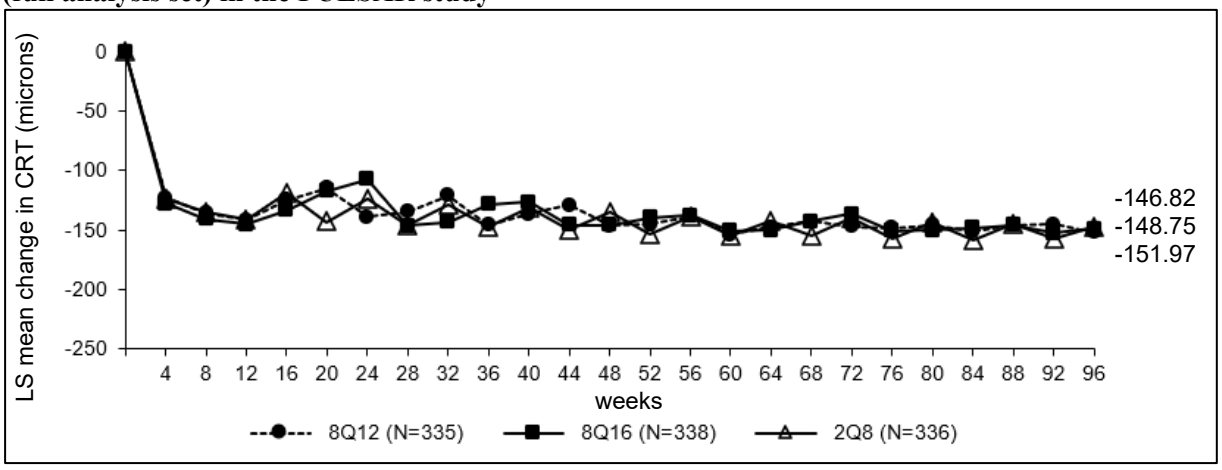
CI: Confidence interval

LS: Least square

SD: Standard deviation

SE: Standard error

Figure 1: LS mean change in central retinal thickness (CRT) from baseline through week 96 (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.

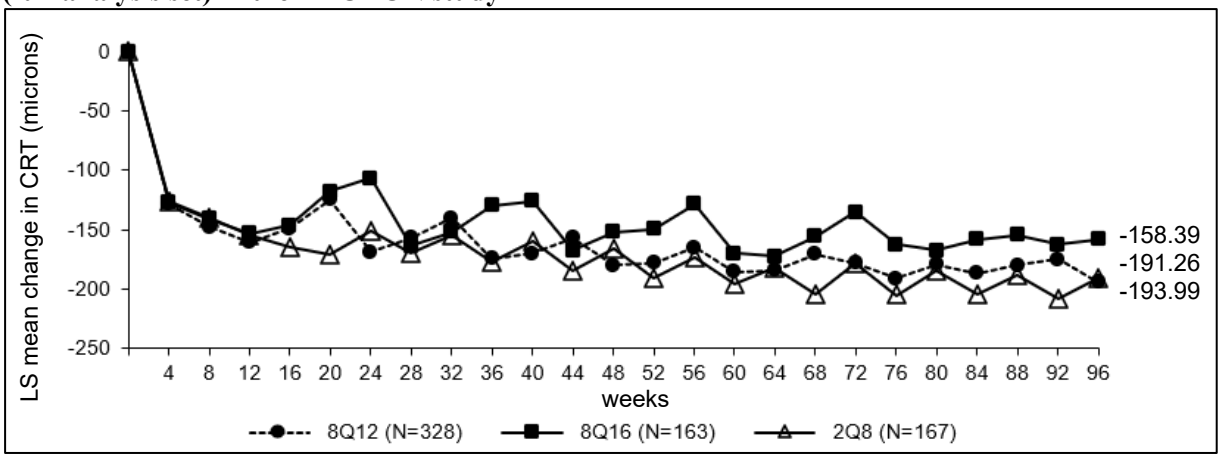
The pharmacodynamic effects of aflibercept 114.3 mg/ml administered every 12 (8Q12) and every 16 (8Q16) weeks are described in comparison with aflibercept 40 mg/ml administered every 8 weeks (2Q8) for the DME indication. These effects are shown as the change in the leakage area from baseline to weeks 48, 60, and 96.

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[A] 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)
	96	-12.8 (10.98)	-9.4 (10.61)	-11.9 (11.26)

[A] based on fluorescein angiography measurement
SD: Standard deviation

Figure 2: LS mean change in central retinal thickness (CRT) from baseline through week 96 (full analysis set) in the PHOTON study



Immunogenicity
After dosing with Eylea 114.3 mg/ml for up to 96 weeks treatment-emergent antibodies to Eylea 114.3 mg/ml were detected in 2.5% to 4.4% 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 treatment interval of 16 weeks, and 38.5% of patients in the 8Q16-group were extended to a treatment interval of 20 weeks.
Patients in the 8Q12-, 8Q16- and 2Q8-groups who completed week 96 received a median (mean) of 9.0 (9.7), 8.0 (8.2) and 13.0 (12.8) injections, respectively.
At week 96, in the pooled 8Q12- and 8Q16-groups 71.0% of patients had attained treatment intervals of ≥16 weeks, 46.8% of patients had attained treatment intervals of ≥20 weeks, and 27.8% of patients had attained treatment intervals of 24 weeks, while maintaining visual and anatomic outcomes.

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’. The treatment effect with Eylea 114.3 mg/ml in mean change in BCVA was maintained through week 96.

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	
Arithmetic mean (SD), observed	96	5.9 (14.2)	5.6 (13.7)	7.4 (13.8)
LS mean (SE) [A]		5.59 (0.77)	5.52 (0.75)	6.60 (0.73)
Difference in LS means (95% CI) [A,B]		-1.01 (-2.82, 0.80)	-1.08 (-2.87, 0.71)	
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%)	
Proportion (LOCF)	96	69.6%	63.6%	66.5%
Adjusted difference in proportion (95% CI) [B,C]		3.0% (-4.1%, 10.1%)	-3.0% (-10.2%, 4.2%)	

Efficacy outcomes	Week	Eylea 8Q12 (N = 335)	Eylea 8Q16 (N = 338)	Eylea 2Q8 (N = 336)
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%)	
Proportion (LOCF)	96	53.3%	53.1%	56.7%
Adjusted difference in proportion (95% CI) [B,C]		-2.7% (-9.4%, 4.0%)	-2.4% (-9.1%, 4.2%)	
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%)	
Proportion (LOCF)	96	22.2%	22.8%	24.2%
Adjusted difference in proportion (95% CI) [B,C]		-2.4% (-8.4%, 3.6%)	-2.0% (-8.0%, 4.1%)	
Last intended treatment intervals				
Patients at ≥Q12 treatment interval [E]				
Proportion (pooled 8Q12- and 8Q16-groups)	96	87.8%		n/a
Proportion		86.6%	89.0%	n/a
Patients at ≥Q16 treatment interval [E]				
Proportion (pooled 8Q12- and 8Q16-groups)	96	71.0%		n/a
Proportion		63.6%	78.4%	n/a
Patients at ≥Q20 treatment interval [E]				
Proportion (pooled 8Q12- and 8Q16-groups)	96	46.8%		n/a
Proportion		40.5%	53.1%	n/a
Patients at Q24 treatment interval [E]				
Proportion (pooled 8Q12- and 8Q16-groups)	96	27.8%		n/a
Proportion		24.7%	30.8%	n/a

[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

[E] Safety analysis set; patients considered as completer for the respective timepoint

CI: Confidence interval

LOCF: Last observation carried forward

LS: Least square

SD: Standard deviation

SE: Standard error

Treatment intervals were analysed in a pre-specified exploratory manner.

Figure 3: LS mean change in BCVA as measured by ETDRS letter score from baseline through week 96 (full analysis set) in the PULSAR study

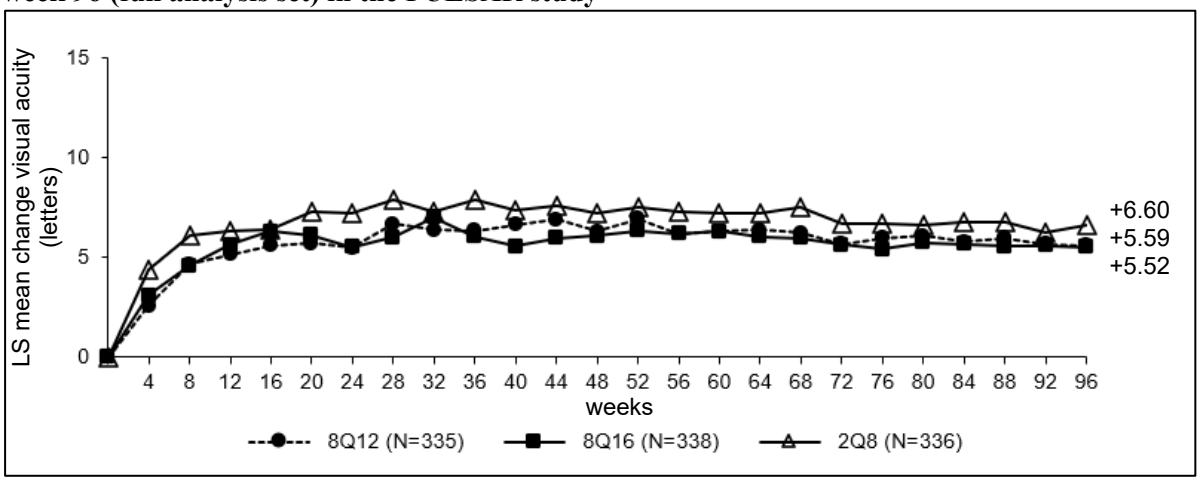
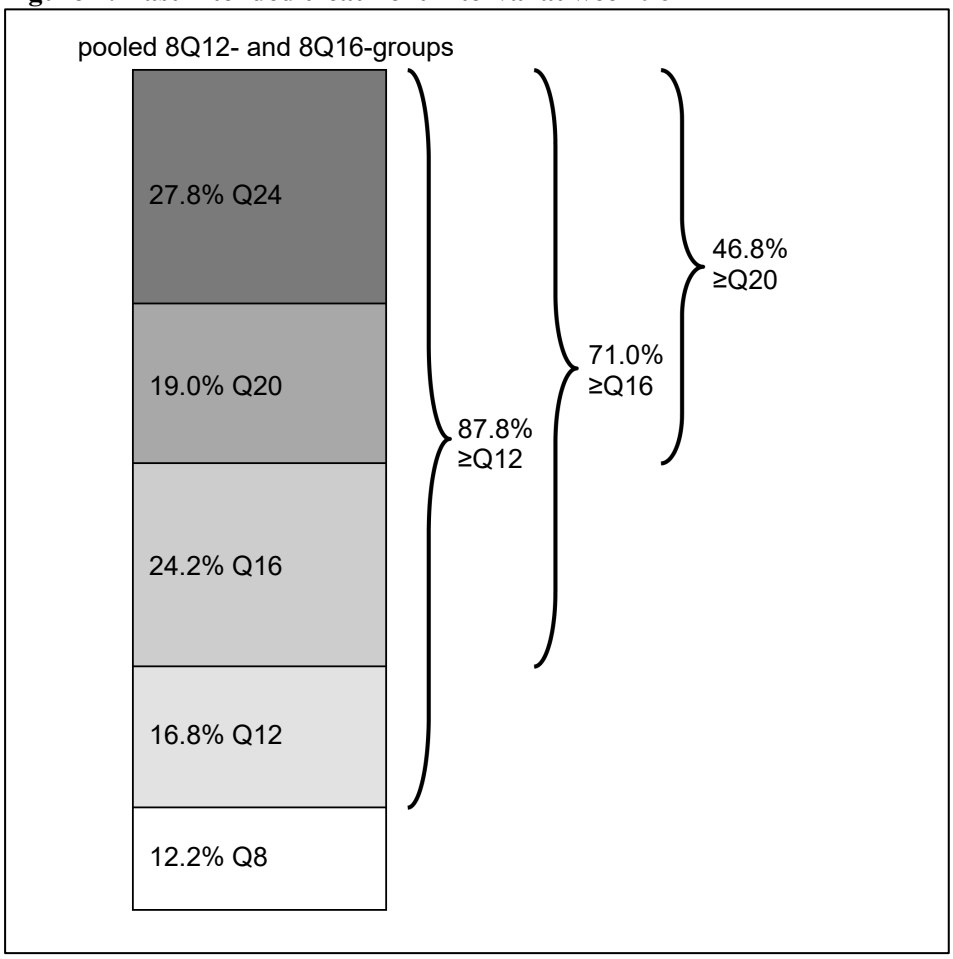


Figure 4: Last intended treatment interval at week 96



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 and week 96 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 96.

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 (8Q12) or 16 weeks (8Q16) 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 8Q16-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 treatment interval of 16 weeks, and 34.2% of patients in the 8Q16-group were extended to a treatment interval of 20 weeks.
Patients in the 8Q12-, 8Q16- and 2Q8-groups who completed week 96 received a median (mean) of 9.0 (9.5), 8.0 (7.8) and 14.0 (13.8) injections, respectively.
At week 96, in the pooled 8Q12- and 8Q16-groups 72.4% of patients had attained treatment intervals of ≥16 weeks, 44.3% of patients had attained treatment intervals of ≥20 weeks, and 26.8% of patients had attained treatment intervals of 24 weeks, while maintaining visual and anatomic outcomes.

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'. The treatment effect with Eylea 114.3 mg/ml in mean change in BCVA was maintained through week 96.

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	
Arithmetic mean (SD), observed	96	8.82 (9.93)	7.50 (9.86)	8.41 (11.10)
LS mean (SE) [A]		8.15 (0.63)	6.59 (0.77)	7.70 (0.89)
Difference in LS means (95% CI) [A,B]		-0.45 (-1.55, 2.45)	-1.11 (-3.27, 1.05)	
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%)	
Proportion (LOCF)	96	66.9%	61.3%	63.0%
Adjusted difference in proportion (95% CI) [B,C]		4.01% (-4.99%, 13.01%)	-1.51% (-11.91%, 8.89%)	
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%)	
Proportion (LOCF)	96	24.5%	19.6%	26.1%
Adjusted difference in proportion (95% CI) [B,C]		-1.88% (-10.03%, 6.28%)	-7.07% (-15.94%, 1.80%)	

Efficacy outcomes	Week	Eylea 8Q12 (N = 328)	Eylea 8Q16 (N = 163)	Eylea 2Q8 (N = 167)
Last intended treatment intervals				
Patients at ≥Q12 treatment interval [E]				
Proportion (pooled 8Q12- and 8Q16-groups)	96	92.9%		n/a
Proportion		91.8%	95.0%	n/a
Patients at ≥Q16 treatment interval [E]				
Proportion (pooled 8Q12- and 8Q16-groups)	96	72.4%		n/a
Proportion		64.1%	87.8%	n/a
Patients at ≥Q20 treatment interval [E]				
Proportion (pooled 8Q12- and 8Q16-groups)	96	44.3%		n/a
Proportion		43.0%	46.8%	n/a
Patients at Q24 treatment interval [E]				
Proportion (pooled 8Q12- and 8Q16-groups)	96	26.8%		n/a
Proportion		23.8%	32.4%	n/a

[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

[E] Safety analysis set; patients considered as completer for the respective timepoint

CI: Confidence interval

LOCF: Last observation carried forward

LS: Least square

SD: Standard deviation

SE: Standard error

Treatment intervals were analysed in a pre-specified exploratory manner.

Figure 5: LS mean change in BCVA as measured by ETDRS letter score from baseline through week 96 (full analysis set) in the PHOTON study

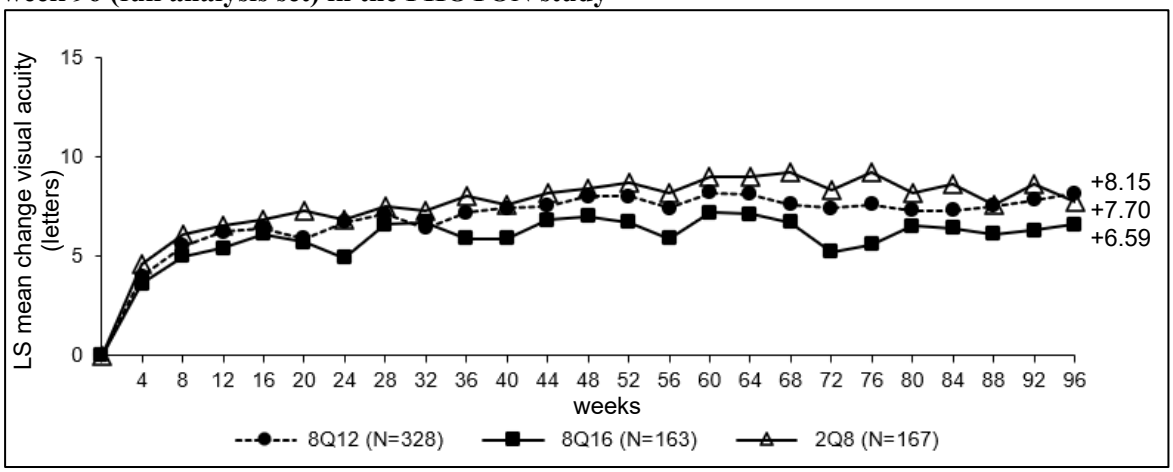
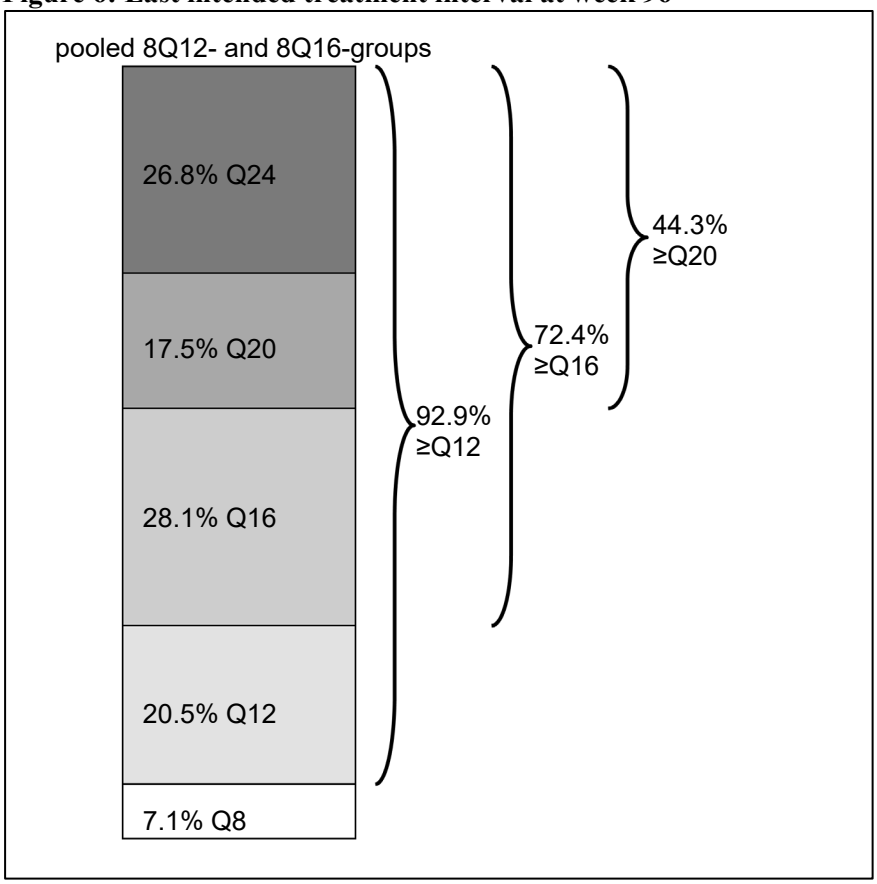


Figure 6: Last intended treatment interval at week 96



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 and week 96 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 96.

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

Eylea 114.3 mg/ml solution for injection

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Prior to usage, the unopened vial may be stored outside the refrigerator below 25 °C for up to 24 hours.

Eylea 114.3 mg/ml solution for injection in pre-filled syringe

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the pre-filled syringe in its blister and in the outer carton in order to protect from light.
Prior to usage, the unopened blister may be stored outside the refrigerator below 25 °C for up to 24 hours.

6.5 Nature and contents of container

Eylea 114.3 mg/ml solution for injection

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.

Eylea 114.3 mg/ml solution for injection in pre-filled syringe

Pre-filled syringe (type I glass) with a grey plunger stopper (elastomeric rubber), a white Luer-lock adaptor with a grey tip cap (elastomeric rubber) and a blue OcuClick dosing system (PC/ABS plastic).
Each pre-filled syringe contains 0.184 ml solution.
Pack size of 1 pre-filled syringe.

6.6 Special precautions for disposal and other handling

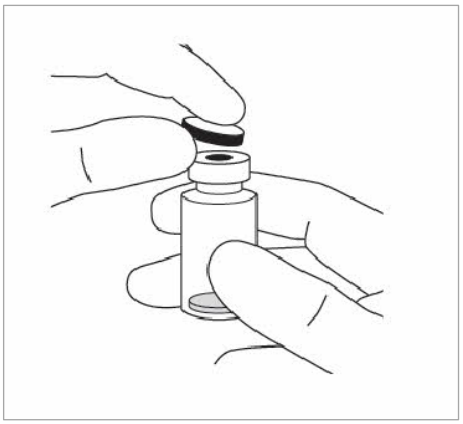
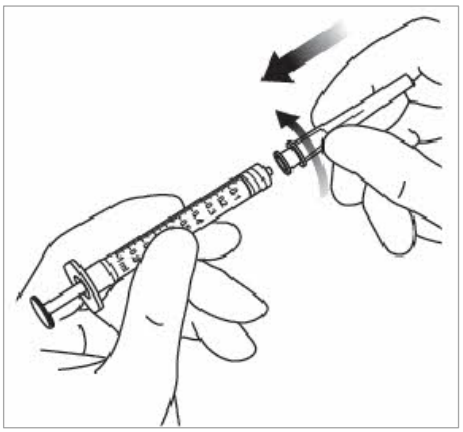
Eylea 114.3 mg/ml solution for injection

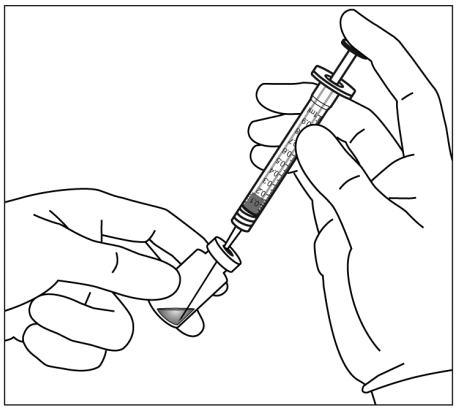
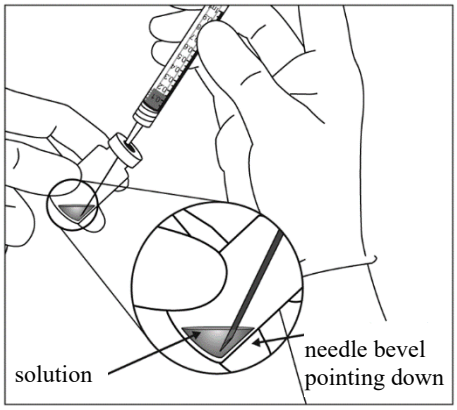
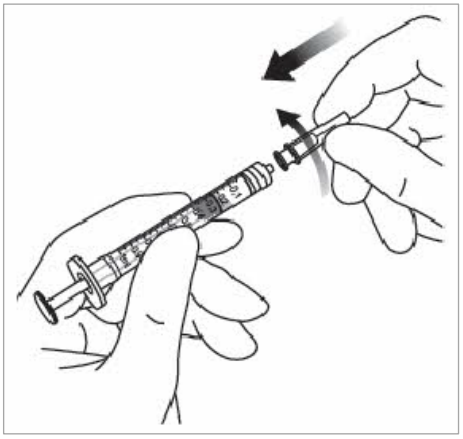
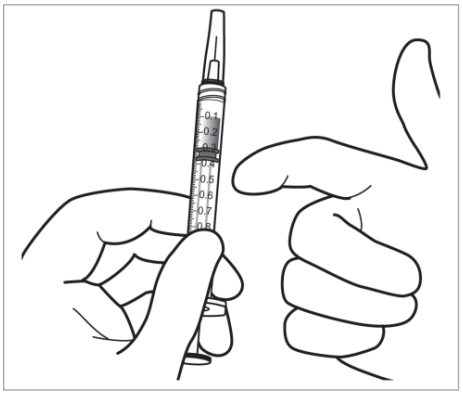
The vial is for single use in one eye only. Extraction of multiple doses from a single vial may increase the risk of contamination and subsequent infection.

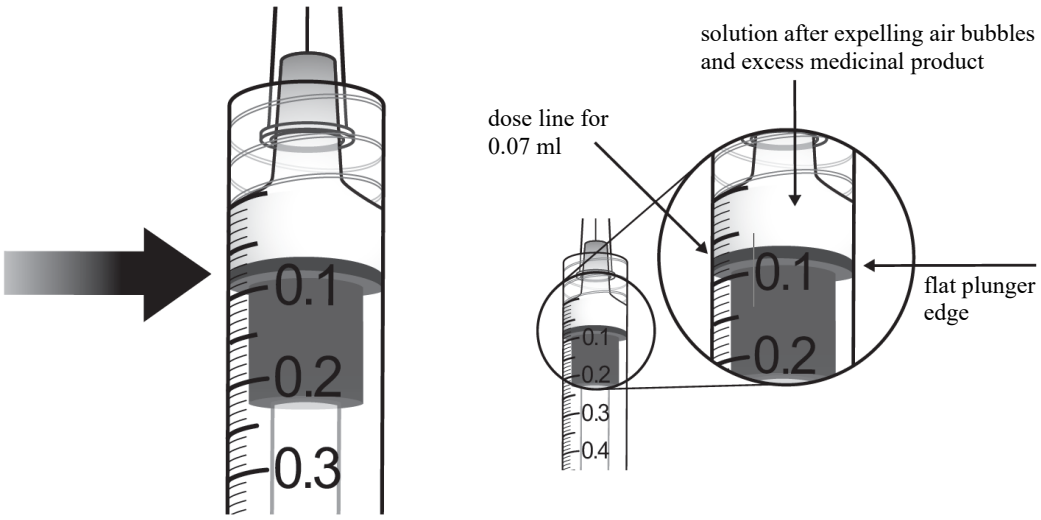
Do not use if the package or its components are expired, damaged, or have been tampered with. Check the label on the vial to make sure you have the strength of Eylea that you intended to use. The 8 mg dose requires use of the Eylea 114.3 mg/ml vial.

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). Use of a smaller size needle (higher gauge) than the recommended 30 G × ½ inch injection needle may result in increased injection forces.

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.
	

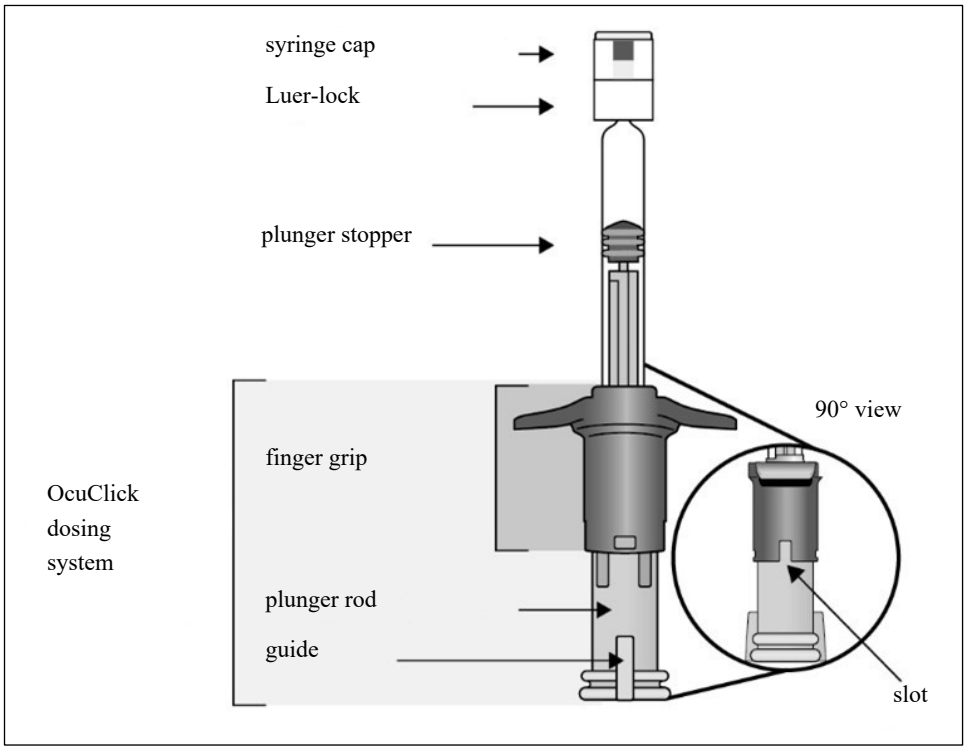
Eylea 114.3 mg/ml solution for injection in pre-filled syringe

The pre-filled syringe with OcuClick dosing system is for single use in one eye only. Extraction of multiple doses from a single pre-filled syringe with OcuClick dosing system may increase the risk of contamination and subsequent infection.

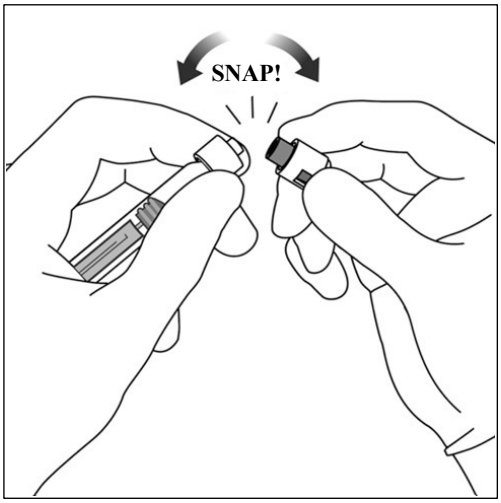
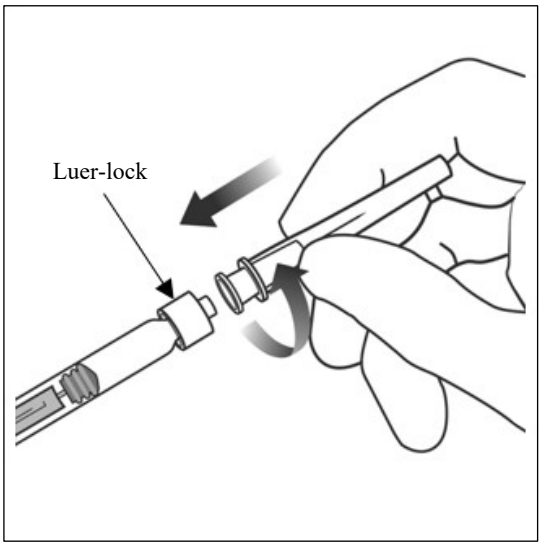
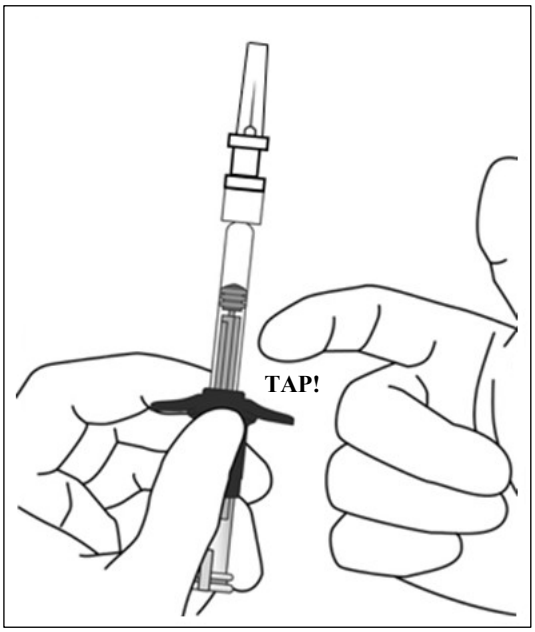
Do not use if the package or its components are expired, damaged, or have been tampered with. Check the label on the pre-filled syringe with OcuClick dosing system to make sure you have the strength of Eylea that you intended to use. The 8 mg dose requires use of the Eylea 114.3 mg/ml pre-filled syringe.

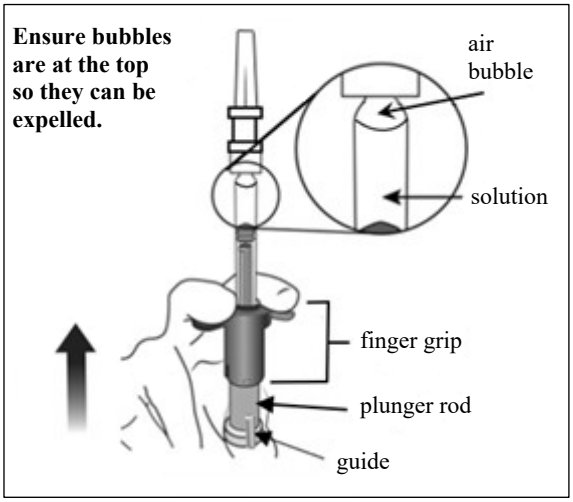
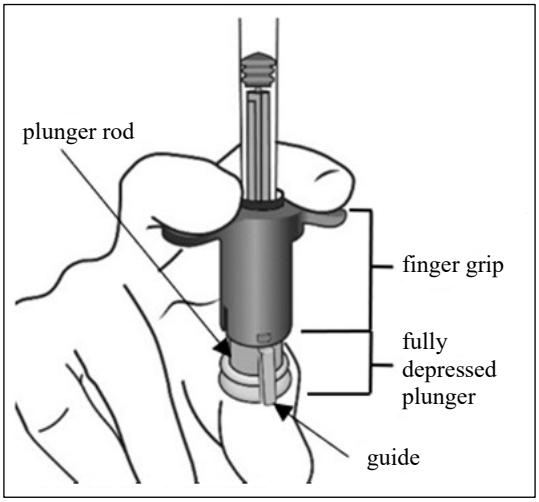
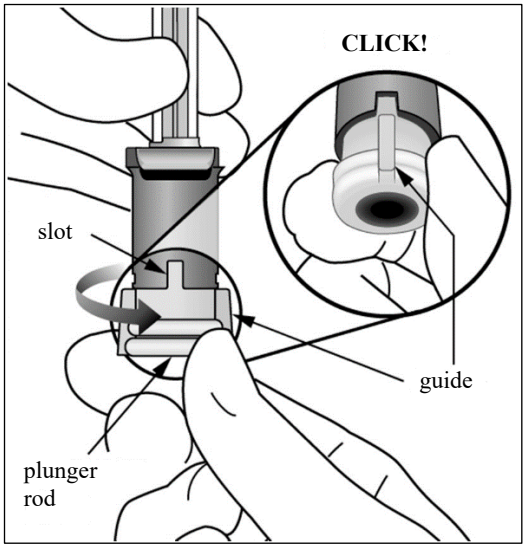
The intravitreal injection should be performed with a 30 G × ½ inch injection needle (not included). Use of a smaller size needle (higher gauge) than the recommended 30 G × ½ inch injection needle may result in increased injection forces.

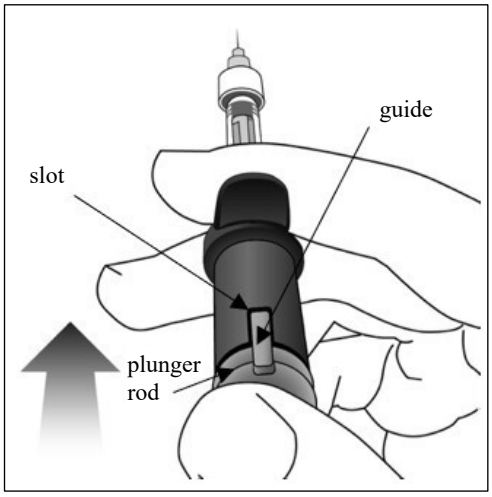
Pre-filled syringe with integrated OcuClick dosing system description



1.	Prepare When ready to administer Eylea 114.3mg/ml, open the carton and remove the sterile blister. Carefully peel open the blister ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready to attach the injection needle. Use aseptic technique to carry out steps 2-9.
2.	Remove syringe Remove the syringe from the sterilised blister.
3.	Inspect syringe and solution for injection **Do not** use the pre-filled syringe if - particulates, cloudiness, or discolouration are visible - any part of the pre-filled syringe with OcuClick dosing system is damaged or loose - the syringe cap is detached from the Luer-lock.

4.	Snap off syringe cap To **snap off** (do not twist off) the syringe cap, hold the syringe in one hand and the syringe cap with the thumb and forefinger of the other hand. **Note:** Do not pull back on the plunger rod. 
5.	Attach needle Firmly twist the 30 G × ½ inch injection needle onto the Luer-lock syringe tip. 
6.	Dislodge air bubbles 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. 

7.	Expel air and excess volume to prime The syringe does not have a dose line because it is designed to set the dose mechanically as explained in the steps below. Priming and setting the dose must be done using the following steps. To eliminate all bubbles and to expel excess medicinal product, slowly depress the plunger rod (left picture below) until it stops, i.e. when the guide on the plunger rod reaches the finger grip (right picture below).  
8.	Set the dose Turn the end of the plunger rod 90 degrees clockwise or counter clockwise until the guide of the plunger rod aligns with the slot. You may hear a 'click'. **Note:** Now the device is ready to dose. Do not push the plunger rod before insertion into the eye. 

9.	Administer the injection Insert the needle into the ocular injection site. Inject the solution by pushing in the plunger rod until it stops, i.e. until the guide is completely within the slot. Do not apply additional pressure once the guide is within the slot. It is normal to see a small amount of residual solution left in the syringe. 
10.	The pre-filled syringe is for single dose administration and single use only. After injection discard the used syringe into a sharps container.

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 - Eylea 114.3 mg/ml solution for injection
EU/1/12/797/004 - Eylea 114.3 mg/ml solution for injection in pre-filled syringe

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

08/2024

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Regeneron Pharmaceuticals, Inc.
81 Columbia Turnpike
Rensselaer, New York 12144
USA

Name and address of the manufacturer responsible for batch release

Bayer AG
Müllerstraße 178
13353 Berlin
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1 of the Marketing Authorisation is in place and functioning before and whilst the medicinal product is on the market.

- **Additional risk minimisation measures**

The MAH has agreed to provide EU educational material for Eylea. Prior to launch and during the product's lifecycle in each Member State the MAH will agree the final educational material with the National Competent Authority.
The MAH ensures that, following discussions and agreement with the National Competent Authorities in each Member State where Eylea is marketed, ophthalmological clinics where Eylea is expected to be used are provided with an updated physician information pack containing the following elements:

- Physician information
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information packs (for adult population only)

The physician information in the educational material contains the following key elements:

- Techniques for the intravitreal injection including use of a 30 G needle, and angle of injection
- The vial and the pre-filled syringe are for single use only
- The need to expel excess volume of the syringe before injecting Eylea to avoid overdose (in adult population only)
- Patient monitoring after intravitreal injection including monitoring for visual acuity and increase of intraocular pressure post-injection
- Key signs and symptoms of intravitreal injection related adverse events including endophthalmitis, intraocular inflammation, increased intraocular pressure, retinal pigment epithelial tear and cataract
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eylea (in adult population only)

The following key elements are specific to the ROP (retinopathy of prematurity) indication:

- Use of the paediatric dosing device is mandatory
- The need to properly prime the paediatric dosing device before injection
- The paediatric dosing device is for single use only

The patient information pack of the educational material for the adult population includes a patient information guide and its audio version. The patient information guide contains following key elements:

- Patient information leaflet
- Who should be treated with Eylea
- How to prepare for Eylea treatment
- What are the steps following treatment with Eylea
- Key signs and symptoms of serious adverse events including endophthalmitis, intraocular inflammation, intraocular pressure increased, retinal pigment epithelial tear and cataract
- When to seek urgent attention from their health care provider
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eylea

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON
Pre-filled syringe

1. NAME OF THE MEDICINAL PRODUCT

Eylea 40 mg/mL solution for injection in pre-filled syringe
aflibercept

2. STATEMENT OF ACTIVE SUBSTANCE

1 pre-filled syringe contains 3.6 mg aflibercept in 0.09 mL solution (40 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: E 432; sodium dihydrogen phosphate, monohydrate; disodium hydrogen phosphate, heptahydrate; sodium chloride; sucrose; water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe contains 3.6 mg aflibercept in 0.09 mL solution (40 mg/mL) .
Delivers 1 single dose of 2 mg/0.05 mL.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravitreal use.
For single use only.
Read the package leaflet before use.
Open the sterile blister in clean administration room only.
Excess volume to be expelled before injecting.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/797/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE BLISTER FOIL
Pre-filled syringe

1. NAME OF THE MEDICINAL PRODUCT

Eylea 40 mg/mL solution for injection
aflibercept

2. STATEMENT OF ACTIVE SUBSTANCE

1 pre-filled syringe contains 3.6 mg aflibercept in 0.09 mL solution (40 mg/mL).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled syringe contains 3.6 mg aflibercept in 0.09 mL solution (40 mg/mL).
Delivers 1 single dose of 2 mg/0.05 mL.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravitreal use.
For single use only.
Read the package leaflet before use.
Open the sterile blister in clean administration room only.
Excess volume to be expelled before injecting.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/797/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS LABEL
Pre-filled syringe

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Eylea 40 mg/mL injection
aflibercept
Intravitreal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Extractable volume 0.09 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON
Vial

1. NAME OF THE MEDICINAL PRODUCT

Eylea 40 mg/mL solution for injection in a vial

aflibercept

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial contains 4 mg aflibercept in 0.1 mL solution (40 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: E 432; sodium dihydrogen phosphate, monohydrate; disodium hydrogen phosphate, heptahydrate, sodium chloride; sucrose; water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial contains 4 mg aflibercept in 0.1 mL solution (40 mg/mL).

18G filter needle

Delivers 1 single dose of 2 mg/0.05 mL.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravitreal use.
For single use only.
Read the package leaflet before use.
Excess volume to be expelled before injecting.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/797/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS LABEL
Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Eylea 40 mg/mL injection
aflibercept
Intravitreal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Extractable volume 0.1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - VIAL

1. NAME OF THE MEDICINAL PRODUCT

Eylea 114.3 mg/ml solution for injection
aflibercept

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial contains 30.1 mg aflibercept in 0.263 ml solution (114.3 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: sucrose, arginine hydrochloride, histidine hydrochloride monohydrate, histidine, polysorbate 20, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial contains 30.1 mg aflibercept in 0.263 ml solution (114.3 mg/ml)
18 G filter needle

5. METHOD AND ROUTE OF ADMINISTRATION

Intravitreal use
For single use only.
Read the package leaflet before use.
30.1 mg/0.263 ml
Single dose: 8 mg/0.07 ml
Excess volume to be expelled before injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/12/797/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL - VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Eylea 114.3 mg/ml injection
aflibercept
Intravitreal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30.1 mg/0.263 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Eylea 114.3 mg/ml solution for injection in pre-filled syringe
aflibercept

2. STATEMENT OF ACTIVE SUBSTANCE

1 pre-filled syringe contains 21 mg aflibercept in 0.184 ml solution (114.3 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: sucrose, arginine hydrochloride, histidine hydrochloride monohydrate, histidine, polysorbate 20, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe with OcuClick dosing system

5. METHOD AND ROUTE OF ADMINISTRATION

Intravitreal use
For single use only.
Read the package leaflet before use.
21 mg/0.184 ml
Single dose: 8 mg/0.07 ml
Excess volume to be expelled before injection.
Read all instructions to apply the correct dose.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/12/797/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINUMUM PARTICULARS TO APPEAR ON THE OUTER PACKGING

PEEL-OFF LABEL AFFIXED TO INNER LID OF CARTON - PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Eylea 114.3 mg/ml

2. EXPIRY DATE

EXP

3. BATCH NUMBER

Lot

PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL – PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Eylea 114.3 mg/ml solution for injection in pre-filled syringe
aflibercept

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

21 mg/0.184 ml

Single dose: 8 mg/0.07 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL - PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Eylea 114.3 mg/ml injection
aflibercept
Intravitreal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

21 mg/0.184 ml

6. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the adult patient

Eylea 40 mg/mL solution for injection in a pre-filled syringe
aflibercept

ADULTS

For information for guardians of babies born prematurely, please see the other side of this package leaflet. [applicable for 1 language]

For information for guardians of babies born prematurely, please see further down the page. [applicable for 2 or more languages]

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Eylea is and what it is used for

Eylea is a solution which is injected into the eye to treat eye conditions in adults called
- neovascular (wet) age-related macular degeneration (wet AMD),
- impaired vision due to macular oedema secondary to retinal vein occlusion (branch RVO (BRVO) or central RVO (CRVO)),
- impaired vision due to diabetic macular oedema (DME),
- impaired vision due to myopic choroidal neovascularisation (myopic CNV).

Aflibercept, the active substance in Eylea, blocks the activity of a group of factors, known as Vascular Endothelial Growth Factor A (VEGF-A) and Placental Growth Factor (PlGF).

In patients with wet AMD and myopic CNV, these factors, in excess are involved in the abnormal formation of new blood vessels in the eye. These new blood vessels can cause the leak of blood components into the eye and eventual damage to tissues in the eye responsible for vision.

In patients with CRVO, a blockage occurs in the main blood vessel that transports blood away from the retina. VEGF levels are elevated in response causing the leakage of fluid into the retina and thereby causing a swelling of the macula, (the portion of the retina responsible for fine vision), which is called macular oedema. When the macula swells with fluid, central vision becomes blurry.

In patients with BRVO, one or more branches of the main blood vessel that transports blood away from the retina is blocked. VEGF levels are elevated in response causing the leakage of fluid into the retina and thereby causing macular oedema.

Diabetic macular oedema 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.

Eylea has been shown to stop the growth of new abnormal blood vessels in the eye which often leak fluid or bleed. Eylea can help to stabilise, and in many cases, improve the vision loss related to wet AMD, CRVO, BRVO, DME and myopic CNV.

2. What you need to know before you are given Eylea

You will not be given Eylea
- if you are **allergic** to aflibercept or any of the other ingredients of this medicine (listed in section 6).
- if you have an active or suspected infection in or around the eye (ocular or periocular infection).
- if you have severe inflammation of the eye (indicated by pain or redness).

Warnings and precautions
Talk to your doctor before you are given Eylea
- if you have glaucoma.
- if you have a history of seeing flashes of light or floaters and if you have a sudden increase of size and number of floaters.
- if surgery was performed or is planned on your eye within the previous or next four weeks.
- if you have a severe form of CRVO or BRVO (ischaemic CRVO or BRVO), treatment with Eylea is not recommended.

Furthermore, it is important for you to know that
- the safety and efficacy of Eylea when administered to both eyes at the same time has not been studied and if used in this way may lead to an increased risk of experiencing side effects.
- injections with Eylea may cause an increase in eye pressure (intraocular pressure) in some patients within 60 minutes of the injection. Your doctor will monitor this after each injection.
- if you develop an infection or inflammation inside the eye (endophthalmitis) or other complications, you may have eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, and increased sensitivity to light. It is important to have any symptoms diagnosed and treated as soon as possible.
- your doctor will check whether you have other risk factors that may increase the chance of a tear or detachment of one of the layers at the back of the eye (retinal detachment or tear, and retinal pigment epithelial detachment or tear), in which case Eylea must be given with caution.
- Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk to the unborn child.
- women of childbearing potential have to use effective contraception during treatment and for at least three further months after the last injection of Eylea.

The systemic use of VEGF inhibitors, substances similar to those contained in Eylea, is potentially related to the risk of blood clots blocking blood vessels (arterial thromboembolic events) which may lead to heart attack or stroke. There is a theoretical risk of such events following injection of Eylea into the eye. There are limited data on safety in treating patients with CRVO, BRVO, DME and myopic CNV who have had a stroke or a mini-stroke (transient ischaemic attack) or a heart attack within the last 6 months. If any of these apply to you, Eylea will be given with caution.

There is only limited experience in the treatment of
- patients with DME due to type I diabetes.
- diabetics with very high average blood sugar values (HbA1c over 12%).
- diabetics with an eye disease caused by diabetes called proliferative diabetic retinopathy.

There is no experience in the treatment of
- patients with acute infections.
- patients with other eye conditions such as a detachment of the retina or a hole in the macula.
- diabetics with uncontrolled high blood pressure.
- non-Asian patients with myopic CNV.
- patients previously treated for myopic CNV.
- patients with damage outside the central part of the macula (extrafoveal lesions) for myopic CNV.

If any of the above applies to you, your doctor will consider this lack of information when treating you with Eylea.

Children and adolescents
The use of Eylea in children and adolescents under 18 years of age for indications other than retinopathy of prematurity (ROP) has not been studied.
.
Other medicines and Eylea
Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding
- Women of childbearing potential have to use effective contraception during treatment and for at least three further months after the last injection of Eylea.
- There is no experience of using Eylea in pregnant women. Eylea should not be used during pregnancy unless the potential benefit outweighs the potential risk to the unborn child. If you are pregnant or planning to become pregnant, discuss this with your doctor before treatment with Eylea.
- Small amounts of Eylea may pass into human milk. The effects on breast-fed newborns/infants are unknown. Eylea is not recommended during breast-feeding. If you are a breastfeeding woman, discuss this with your doctor before treatment with Eylea.

Driving and using machines
After your injection with Eylea, you may experience some temporary visual disturbances. Do not drive or use machines as long as these last.

Important information about some of the ingredients of Eylea
This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

3. How you will be given Eylea

A doctor experienced in giving eye injections will inject Eylea into your eye under aseptic (clean and sterile) conditions.

The recommended dose is 2 mg aflibercept (0.05 mL).
Eylea is given as an injection into your eye (intravitreal injection).

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 anaesthetic to reduce or prevent any pain you might have with the injection.

wet AMD
Patients with wet AMD will be treated with one injection per month for three consecutive doses, followed by another injection after a further two months.

Your doctor will then decide whether the treatment interval between injections may be kept at every two months or be gradually extended in 2- or 4-weekly intervals if your condition has been stable.

If your condition worsens, the interval between injections can be shortened.

Unless you experience any problems or are advised differently by your doctor, there is no need for you to see your doctor between the injections.

Macular oedema secondary to RVO (branch RVO or central RVO)
Your doctor will determine the most appropriate treatment schedule for you. You will start your treatment with a series of monthly Eylea injections.

The interval between two injections should not be shorter than one month.

Your doctor may decide to stop treatment with Eylea, if you are not benefiting from continued treatment.

Your treatment will continue with monthly injections until your condition is stable. Three or more monthly injections may be needed.

Your doctor will monitor your response to treatment and may continue your treatment by gradually increasing the interval between your injections to maintain a stable condition. If your condition starts to worsen with a longer treatment interval, your doctor will shorten the interval accordingly.

Based on your response to treatment your doctor will decide on the schedule for follow up examinations and treatments.

Diabetic macular oedema (DME)
Patients with DME will be treated with one injection per month for the first five consecutive doses followed by one injection every two months thereafter.

Treatment interval may be kept at every two months or adjusted to your condition, based on your doctor's examination. Your doctor will decide on the schedule for follow up examinations.

Your doctor may decide to stop treatment with Eylea if it is determined that you are not benefiting from continued treatment.

Myopic CNV
Patients with myopic CNV will be treated with one single injection. You will receive further injections only if your doctor's examinations reveal that your condition has not improved.

The interval between two injections should not be shorter than one month.

If your condition goes away and then comes back, your doctor may re-start the treatment.

Your doctor will decide on the schedule for follow up examinations.

Detailed instructions for use are given at the end of the leaflet under "How to prepare and administer Eylea to adults".

If a dose of Eylea is missed
Make a new appointment for an examination and injection.

Stopping treatment with Eylea
Consult your doctor before stopping the treatment.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions (hypersensitivity) could potentially occur. **These may be serious and require that you contact your doctor immediately.**

With administration of Eylea, there may be some side effects affecting the eyes which are due to the injection procedure. Some of these may be **serious** and include **blindness**, **a serious infection or inflammation inside the eye** (endophthalmitis), **detachment**, **tear or bleeding of the light-sensitive layer at the back of the eye** (retinal detachment or tear), **clouding of the lens** (cataract), **bleeding in the eye** (vitreous haemorrhage), **detachment of the gel-like substance inside the eye from the retina** (vitreous detachment) and **increase of pressure inside the eye**, see section 2. These serious side effects affecting the eyes occurred in less than 1 in 1,900 injections in clinical studies.

If you experience a sudden decrease in vision, or an increase in pain and redness in your eye after your injection, **contact your doctor immediately**.

List of side effects reported
The following is a list of the side effects reported to be possibly related to the 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.

Very common side effects (may affect more than 1 in 10 people):
- deterioration of eyesight
- bleeding in the back of the eye (retinal haemorrhage)
- bloodshot eye caused by bleeding from small blood vessels in the outer layers of the eye
- eye pain

Common side effects (may affect up to 1 in 10 people):
- detachment or tear of one of the layers in the back of the eye, resulting in flashes of light with floaters sometimes progressing to a loss of vision (retinal pigment epithelial tear*/detachment, retinal detachment/tear)
    - *Conditions known to be associated with wet AMD; observed in wet AMD patients only.
- degeneration of the retina causing disturbed vision
- bleeding in the eye (vitreous haemorrhage)
- certain forms of clouding of the lens (cataract)
- damage to the front layer of the eyeball (the cornea)
- increase in eye pressure
- moving spots in vision (floaters)
- detachment of the gel-like substance inside the eye from the retina (vitreous detachment, resulting in flashes of light with floaters)
- a feeling of having something in the eye
- increased tear production
- swelling of the eyelid
- bleeding at the injection site
- redness of the eye

Uncommon side effects (may affect up to 1 in 100 people):
- allergic reactions (hypersensitivity)**
  - ** Allergic reactions like rash, itching (pruritus), hives (urticaria), and a few cases of severe allergy (anaphylactic/anaphylactoid) reactions were reported.
- serious inflammation or infection inside the eye (endophthalmitis)
- inflammation in the iris or other parts of the eye (iritis, uveitis, iridocyclitis, anterior chamber flare)
- abnormal sensation in the eye
- eyelid irritation
- swelling of the front layer of the eyeball (cornea)

Rare side effects (may affect up to 1 in 1,000 people):
- blindness
- clouding of the lens due to injury (traumatic cataract)
- inflammation of the gel-like substance inside the eye
- pus in the eye

In the clinical trials, there was an increased incidence of bleeding from small blood vessels in the outer layers of the eye (conjunctival haemorrhage) in patients with wet AMD receiving blood thinners. This increased incidence was comparable between patients treated with ranibizumab and Eylea.

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

As with all therapeutic proteins, there is a possibility for an immune reaction (formation of antibodies) with Eylea.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via

België
Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten – www.fagg.be
Afdeling Vigilantie
Website: www.eenbijwerkingmelden.be
e-mail: adr@fagg.be

Luxemburg
Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé
Site internet : www.guichet.lu/pharmacovigilance

Nederland
Nederlands Bijwerkingen Centrum Lareb
Website: www.lareb.nl

By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Eylea

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2 °C to 8 °C). Do not freeze.
- The unopened blister may be stored outside the refrigerator below 25 °C for up to 24 hours.
- Store in the original package in order to protect from light.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away any medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Eylea contains
- The active substance is: aflibercept. One pre-filled syringe contains an extractable volume of at least 0.09 mL, equivalent to at least 3.6 mg aflibercept. One pre-filled syringe delivers a dose of 2 mg aflibercept in 0.05 mL.
- The other ingredients are: polysorbate 20 (E 432), sodium dihydrogen phosphate monohydrate (for pH adjustment), disodium hydrogen phosphate heptahydrate (for pH adjustment), sodium chloride, sucrose, water for injections.

What Eylea looks like and contents of the pack
Eylea is a solution for injection (injection) in a pre-filled syringe. The solution is colourless to pale yellow.
Pack size of 1 pre-filled syringe.

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
Germany

Manufacturer
Bayer AG
Müllerstraße 178
13353 Berlin
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Luxemburg	**Nederland**
Bayer SA-NV	Bayer B.V.
Tél/Tel: +32-(0)2-535 63 11	Tel: +31–(0)23-799 1000

This leaflet was last revised in 08/2024

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

How to prepare and administer Eylea to adults

The pre-filled syringe should only be used **for the treatment of a single eye.**
Do not open the sterile pre-filled syringe blister outside the clean administration room.

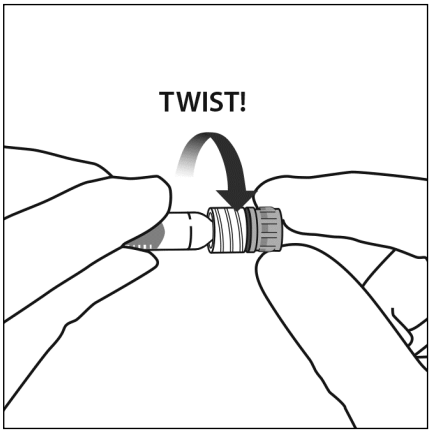
The pre-filled syringe contains more than the recommended dose of 2 mg aflibercept (equivalent to 0.05 mL). The excess volume must be discarded prior to administration.

The solution should be inspected visually for any foreign particulate matter and/or discolouration or any variation in physical appearance prior to administration. In the event of either being observed, discard the medicinal product.

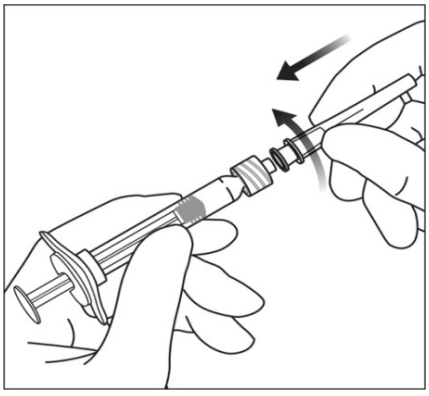
The unopened blister may be stored outside the refrigerator below 25 °C for up to 24 hours. After opening the blister, proceed under aseptic conditions. For the intravitreal injection, a 30 G x ½ inch injection needle should be used.

Instructions for use of pre-filled syringe:

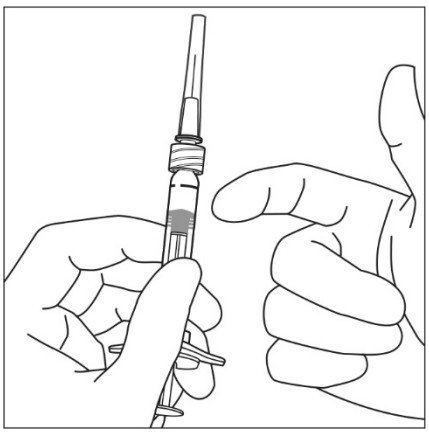
1. When ready to administer Eylea, open the carton and remove the sterilised blister. Carefully peel open the blister ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready for assembly.
2. Using aseptic technique, remove the syringe from the sterilised blister.
3. To remove the syringe cap, hold the syringe in one hand while using the other hand to grasp the syringe cap with the thumb and fore finger. Please note: You should twist off (do not snap off) the syringe cap.



4. To avoid compromising the sterility of the product, do not pull back on the plunger.
5. Using aseptic technique, firmly twist the injection needle onto the Luer-lock syringe tip.

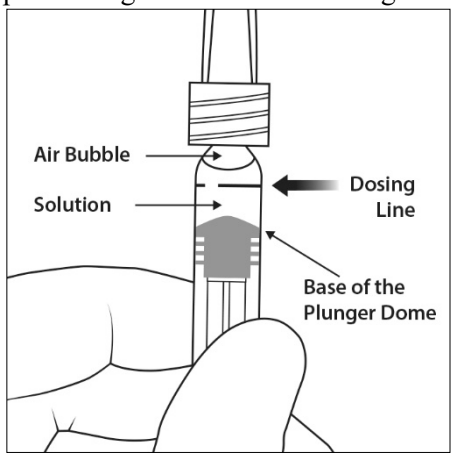


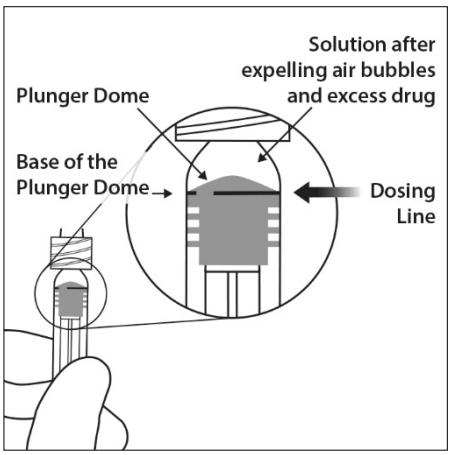
6. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



7. Eliminate all bubbles and **expel excess medicinal product by slowly depressing the plunger to align the base of the plunger dome (not the tip of the dome) with the dosing line on the syringe** (equivalent to 0.05 mL i.e. 2 mg aflibercept).

Note: This accurate positioning of the plunger is very important, because incorrect plunger positioning can lead to delivering more or less than the labelled dose





8. Inject while pressing the plunger carefully and with constant pressure. Do not apply additional pressure once the plunger has reached the bottom of the syringe. **Do not administer any residual solution observed in the syringe**.

9. The pre-filled syringe is for single use only. Extraction of multiple doses from a pre-filled syringe may increase the risk of contamination and subsequent infection.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package Leaflet: Information for guardians of babies born prematurely

Eylea 40 mg/mL solution for injection in a pre-filled syringe
aflibercept

BABIES BORN PREMATURELY

For adult information, please see the other side of this package leaflet. [applicable for 1 language]

For adult information, please see top of the page. [applicable for 2 or more languages]

Read all of this leaflet carefully before the baby is given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask the baby's doctor.
- If you notice any symptoms of side effects, talk to the baby's doctor. This includes any possible symptoms and side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Eylea is and what it is used for

Eylea is a solution which is injected into the eye. Eylea belongs to a group of medicines called antineovascularisation agents. It contains the active substance called aflibercept.

Eylea is used in babies born prematurely to treat an eye condition called retinopathy of prematurity (ROP). Babies with ROP have abnormal growth of new blood vessels in the back of the eye (retina) induced by Vascular Endothelial Growth Factor (VEGF). This may cause vision impairment and in severe cases permanent blindness.

Aflibercept, the active substance in Eylea, blocks the activity of a group of factors, known as Vascular Endothelial Growth Factor A (VEGF-A) and Placental Growth Factor (PlGF).

Eylea has been shown to stop the growth of new abnormal blood vessels in the eye which often leak fluid or bleed. Eylea can help to stabilise, and in many cases, improve the vision loss related to ROP.

2. What you need to know before the baby is given Eylea

The baby will not be given Eylea if he or she
- is **allergic** to aflibercept or any of the other ingredients of this medicine (listed in section 6).
- has an active or suspected infection in or around the eye (ocular or periocular infection).
- has severe inflammation of the eye (indicated by pain or redness).

Warnings and precautions
Talk to the baby's doctor before the baby is given Eylea
- if surgery was performed or is planned on the baby's eye within the previous or next four weeks.

Furthermore, it is important for you to know that

- injections with Eylea may cause an increase in eye pressure (intraocular pressure) in some patients within 60 minutes of the injection. The baby's doctor will monitor this after each injection.
- if the baby develops an infection or inflammation inside the eye (endophthalmitis) or other complications, the baby may have **redness/irritation of the eye**, **ocular discharge**, **lid swelling** and **increased sensitivity to light**. It is important to have any symptoms diagnosed and treated as soon as possible.
  Please tell the baby's doctor immediately if the baby develops any signs or symptoms outlined.
- the baby's doctor will check whether the baby has other risk factors that may increase the chance of a tear or detachment of one of the layers at the back of the eye (retinal detachment or tear), in which case Eylea must be given with caution.

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

There is no experience in the treatment of
- patients with acute infections
- patients with other eye conditions such as a detachment of the retina or a hole in the macula

If any of the above applies to the baby, the baby's doctor will consider this lack of information when treating the baby with Eylea.

Other medicines and Eylea
Tell the baby's doctor if the baby is receiving, has recently received or might receive any other medicines.

Important information about some of the ingredients of Eylea
This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

3. How the baby will be given Eylea

A doctor experienced in giving eye injections will inject Eylea into the baby's eyes under aseptic (clean and sterile) conditions.

The recommended dose is 0.4 mg aflibercept (0.01 mL).
Eylea is given as an injection into the baby's eye (intravitreal injection).

Before the injection the baby's doctor will use a disinfectant eyewash to clean the baby's eye carefully to prevent infection. The baby's doctor will also give the baby a local anaesthetic to reduce or prevent any pain the baby might have with the injection.

The treatment is started with a single injection per eye and may be given into the second eye on the same day. The baby's doctor will monitor the condition of the baby's eye(s). Depending on how the baby responds to the treatment, the baby's doctor will decide if and when further treatment is needed. The treatment interval between the 2 doses injected into the same eye should be at least 4 weeks.

Detailed instructions for use are given at the end of the leaflet under "How to prepare and administer Eylea to preterm infants".

Stopping treatment with Eylea
If you are considering stopping Eylea treatment for the baby, please discuss this with the baby's doctor at your next appointment. The baby's doctor will advise you and decide how long the baby should be treated with Eylea.

If you have any further questions on the use of this medicine, ask the baby's doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects reported in more than one baby born prematurely were
- **detachment of the layer in the back of the eye** (retinal detachment)
- **bleeding in the back of the eye** (retinal haemorrhage)
- **bloodshot eye** caused by bleeding from small blood vessels in the outer layers of the eye (conjunctival haemorrhage)
- **bleeding at the injection site** (injection site haemorrhage)
- **increase in eye pressure**
- **swelling of the eyelid** (eyelid oedema)

Additional side effects that have been observed with Eylea **in adults** are listed below. These side effects may also occur in babies born prematurely
- **allergic reactions** (hypersensitivity)

These may be serious and require that you contact the baby's doctor immediately.

Side effects affecting the eyes due to the injection procedure may be **serious** and include
- **blindness**
- a serious **infection or inflammation** inside the eye (endophthalmitis)
- **detachment, tear or bleeding** of the light-sensitive layer at the back of the eye (retinal detachment or tear)
- **clouding of the lens** (cataract)
- **bleeding in the eye** (vitreous haemorrhage)
- **detachment** of the gel-like substance inside the eye from the retina (vitreous detachment)
- **increase of pressure** inside the eye (intraocular pressure increased), see section 2

These serious side effects affecting the eyes occurred in less than 1 in 1,900 injections in clinical studies in adults.

It is important to identify and treat serious side effects such as infection inside the eye or retinal detachment as soon as possible.
Tell the baby's doctor immediately if you notice symptoms in the baby's eye after injection such as
- **redness/irritation**
- **ocular discharge**
- **lid swelling**
- **increased sensitivity to light**

Other side effects observed in adults are described below.

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

Very common side effects (may affect more than 1 in 10 people):
- deterioration of eyesight
- bleeding in the back of the eye (retinal haemorrhage)
- bloodshot eye caused by bleeding from small blood vessels in the outer layers of the eye
- eye pain

Common side effects (may affect up to 1 in 10 people):
- detachment or tear of one of the layers in the back of the eye, resulting in flashes of light with floaters sometimes progressing to a loss of vision (retinal pigment epithelial tear*/detachment, retinal detachment/tear)
    - * Conditions known to be associated with wet age-related macular degeneration (AMD); observed in wet AMD patients only.
- degeneration of the retina causing disturbed vision
- bleeding in the eye (vitreous haemorrhage)
- certain forms of clouding of the lens (cataract)
- damage to the front layer of the eyeball (the cornea)
- increase in eye pressure
- moving spots in vision (floaters)
- detachment of the gel-like substance inside the eye from the retina (vitreous detachment, resulting in flashes of light with floaters)
- a feeling of having something in the eye
- increased tear production
- swelling of the eyelid
- bleeding at the injection site
- redness of the eye

Uncommon side effects (may affect up to 1 in 100 people):
- allergic reactions (hypersensitivity)**
    - ** Allergic reactions like rash, itching (pruritus), hives (urticaria), and a few cases of severe allergy (anaphylactic/anaphylactoid) reactions were reported.
- serious inflammation or infection inside the eye (endophthalmitis)
- inflammation in the iris or other parts of the eye (iritis, uveitis, iridocyclitis, anterior chamber flare)
- abnormal sensation in the eye
- eyelid irritation
- swelling of the front layer of the eyeball (cornea)

Rare side effects (may affect up to 1 in 1,000 people):
- blindness
- clouding of the lens due to injury (traumatic cataract)
- inflammation of the gel-like substance inside the eye
- pus in the eye

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

As with all therapeutic proteins, there is a possibility for an immune reaction (formation of antibodies) with Eylea.

If you have any questions about any side effects, ask the baby’s doctor.

Reporting of side effects
If you observe any side effects in the baby, talk to the baby's doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly

België
Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten – www.fagg.be
Afdeling Vigilantie
Website: www.eenbijwerkingmelden.be
e-mail: adr@fagg.be

Luxemburg
Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé
Site internet : www.guichet.lu/pharmacovigilance

Nederland
Nederlands Bijwerkingen Centrum Lareb
Website: www.lareb.nl

By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Eylea

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2 °C to 8 °C). Do not freeze.
- The unopened blister may be stored outside the refrigerator below 25 ºC for up to 24 hours.
- Store in the original package in order to protect from light.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away any medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Eylea contains
- The active substance is: aflibercept. One pre-filled syringe contains an extractable volume of at least 0.09 mL, equivalent to at least 3.6 mg aflibercept. One pre-filled syringe delivers a single dose of 0.4 mg aflibercept in 0.01 mL.
- The other ingredients are: polysorbate 20 (E 432), sodium dihydrogen phosphate monohydrate (for pH adjustment), disodium hydrogen phosphate heptahydrate (for pH adjustment), sodium chloride, sucrose, water for injections.

What Eylea looks like and contents of the pack
Eylea is a solution for injection (injection) in a pre-filled syringe. The solution is colourless to pale yellow.
Pack size of 1 pre-filled syringe.

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
Germany

Manufacturer

Bayer AG
Müllerstraße 178
13353 Berlin
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Luxemburg	**Nederland**
Bayer SA-NV	Bayer B.V.
Tél/Tel: +32-(0)2-535 63 11	Tel: +31–(0)23-799 1000

This leaflet was last revised in 08/2024

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

How to prepare and administer Eylea to preterm infants

The pre-filled syringe should only be used **for the treatment of a single eye.** Extraction of multiple doses from a pre-filled syringe may increase the risk of contamination and subsequent infection.

Do not open the sterile pre-filled blister outside the clean administration room. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The pre-filled syringe contains more than the recommended dose of 0.4 mg aflibercept (equivalent to 0.01 mL). For treatment of preterm infants, the PICLEO paediatric dosing device in combination with the pre-filled syringe must be used for administration of a single dose of 0.4 mg aflibercept (equivalent to 0.01 mL). See following section "***Instructions for use of pre-filled syringe***".

The solution should be inspected visually for any foreign particulate matter and/or discolouration or any variation in physical appearance prior to administration. In the event of either being observed, discard the medicinal product.

The unopened blister may be stored outside the refrigerator below 25 ºC for up to 24 hours. After opening the blister, proceed under aseptic conditions.
For the intravitreal injection, a 30 G x ½ inch injection needle should be used.

Instructions for use of pre-filled syringe:
To prepare the pre-filled syringe for administration to preterm infants, follow the steps 1 and 2 below and then adhere to the instructions for use included in the package of the PICLEO paediatric dosing device.

1. When ready to administer Eylea, open the carton and remove the sterilised blister. Carefully peel open the blister ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready for assembly.
2. Using aseptic technique, remove the syringe from the sterilised blister.

Package Leaflet: Information for the patient

Eylea 40 mg/mL solution for injection in a vial
aflibercept

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Eylea is and what it is used for

Eylea is a solution which is injected into the eye to treat eye conditions in adults called

- neovascular (wet) age-related macular degeneration (wet AMD),
- impaired vision due to macular oedema secondary to retinal vein occlusion (branch RVO (BRVO) or central RVO (CRVO)),
- impaired vision due to diabetic macular oedema (DME),
- impaired vision due to myopic choroidal neovascularisation (myopic CNV).

Aflibercept, the active substance in Eylea, blocks the activity of a group of factors, known as Vascular Endothelial Growth Factor A (VEGF-A) and Placental Growth Factor (PlGF).

In patients with wet AMD and myopic CNV, these factors, in excess are involved in the abnormal formation of new blood vessels in the eye. These new blood vessels can cause the leak of blood components into the eye and eventual damage to tissues in the eye responsible for vision.

In patients with CRVO, a blockage occurs in the main blood vessel that transports blood away from the retina. VEGF levels are elevated in response causing the leakage of fluid into the retina and thereby causing a swelling of the macula, (the portion of the retina responsible for fine vision), which is called macular oedema. When the macula swells with fluid, central vision becomes blurry.

In patients with BRVO, one or more branches of the main blood vessel that transports blood away from the retina is blocked. VEGF levels are elevated in response causing the leakage of fluid into the retina and thereby causing macular oedema.

Diabetic macular oedema 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.

Eylea has been shown to stop the growth of new abnormal blood vessels in the eye which often leak fluid or bleed. Eylea can help to stabilise, and in many cases, improve the vision loss related to wet AMD, CRVO, BRVO, DME and myopic CNV.

2. What you need to know before you are given Eylea

You will not be given Eylea
- if you are allergic to aflibercept or any of the other ingredients of this medicine (listed in section 6).
- if you have an active or suspected infection in or around the eye (ocular or periocular infection).
- if you have severe inflammation of the eye (indicated by pain or redness).

Warnings and precautions

Talk to your doctor before you are given Eylea:

- if you have glaucoma.
- if you have a history of seeing flashes of light or floaters and if you have a sudden increase of size and number of floaters.
- if surgery was performed or is planned on your eye within the previous or next four weeks.
- if you have a severe form of CRVO or BRVO (ischaemic CRVO or BRVO), treatment with Eylea is not recommended.

Furthermore, it is important for you to know that:

- the safety and efficacy of Eylea when administered to both eyes at the same time has not been studied and if used in this way may lead to an increased risk of experiencing side effects.
- injections with Eylea may cause an increase in eye pressure (intraocular pressure) in some patients within 60 minutes of the injection. Your doctor will monitor this after each injection.
- if you develop an infection or inflammation inside the eye (endophthalmitis) or other complications, you may have eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, and increased sensitivity to light. It is important to have any symptoms diagnosed and treated as soon as possible.
- your doctor will check whether you have other risk factors that may increase the chance of a tear or detachment of one of the layers at the back of the eye (retinal detachment or tear, and retinal pigment epithelial detachment or tear), in which case Eylea must be given with caution.
- Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk to the unborn child.
- women of childbearing potential have to use effective contraception during treatment and for at least three further months after the last injection of Eylea.

The systemic use of VEGF inhibitors, substances similar to those contained in Eylea, is potentially related to the risk of blood clots blocking blood vessels (arterial thromboembolic events) which may lead to heart attack or stroke. There is a theoretical risk of such events following injection of Eylea into the eye. There are limited data on safety in treating patients with CRVO, BRVO, DME and myopic CNV who have had a stroke or a mini-stroke (transient ischaemic attack) or a heart attack within the last 6 months. If any of these apply to you, Eylea will be given with caution.

There is only limited experience in the treatment of
- patients with DME due to type I diabetes.
- diabetics with very high average blood sugar values (HbA1c over 12%).
- diabetics with an eye disease caused by diabetes called proliferative diabetic retinopathy.

There is no experience in the treatment of
- patients with acute infections.
- patients with other eye conditions such as a detachment of the retina or a hole in the macula.
- diabetics with uncontrolled high blood pressure.
- non-Asian patients with myopic CNV.
- patients previously treated for myopic CNV.
- patients with damage outside the central part of the macula (extrafoveal lesions) for myopic CNV.

If any of the above applies to you, your doctor will consider this lack of information when treating you with Eylea.

Children and adolescents
The use of Eylea in children or adolescents under 18 has not been studied because wet AMD, CRVO, BRVO, DME and myopic CNV occur mainly in adults. Therefore, its use in this age group is not relevant.

Other medicines and Eylea
Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding
- Women of childbearing potential have to use effective contraception during treatment and for at least three further months after the last injection of Eylea.

- There is no experience of using Eylea in pregnant women. Eylea should not be used during pregnancy unless the potential benefit outweighs the potential risk to the unborn child. If you are pregnant or planning to become pregnant, discuss this with your doctor before treatment with Eylea.

- Small amounts of Eylea may pass into human milk. The effects on breast-fed newborns/infants are unknown. Eylea is not recommended during breast-feeding. If you are a breastfeeding woman, discuss this with your doctor before treatment with Eylea.

Driving and using machines
After your injection with Eylea, you may experience some temporary visual disturbances. Do not drive or use machines as long as these last.

Important information about some of the ingredients of Eylea
This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

3. How you will be given Eylea

A doctor experienced in giving eye injections will inject Eylea into your eye under aseptic (clean and sterile) conditions.

The recommended dose is 2 mg aflibercept (0.05 mL).
Eylea is given as an injection into your eye (intravitreal injection).

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 anaesthetic to reduce or prevent any pain you might have with the injection.

wet AMD

Patients with wet AMD will be treated with one injection per month for three consecutive doses, followed by another injection after a further two months.

Your doctor will then decide whether the treatment interval between injections may be kept at every two months or be gradually extended in 2- or 4-weekly intervals if your condition has been stable.

If your condition worsens, the interval between injections can be shortened.

Unless you experience any problems or are advised differently by your doctor, there is no need for you to see your doctor between the injections.

Macular oedema secondary to RVO (branch RVO or central RVO)

Your doctor will determine the most appropriate treatment schedule for you. You will start your treatment with a series of monthly Eylea injections.

The interval between two injections should not be shorter than one month.

Your doctor may decide to stop treatment with Eylea, if you are not benefiting from continued treatment.

Your treatment will continue with monthly injections until your condition is stable. Three or more monthly injections may be needed.

Your doctor will monitor your response to treatment and may continue your treatment by gradually increasing the interval between your injections to maintain a stable condition. If your condition starts to worsen with a longer treatment interval, your doctor will shorten the interval accordingly.

Based on your response to treatment your doctor will decide on the schedule for follow up examinations and treatments.

Diabetic macular oedema (DME)

Patients with DME will be treated with one injection per month for the first five consecutive doses followed by one injection every two months thereafter.

Treatment interval may be kept at every two months or adjusted to your condition, based on your doctor's examination. Your doctor will decide on the schedule for follow up examinations.

Your doctor may decide to stop treatment with Eylea if it is determined that you are not benefiting from continued treatment.

Myopic CNV

Patients with myopic CNV will be treated with one single injection. You will receive further injections only if your doctor's examinations reveal that your condition has not improved.

The interval between two injections should not be shorter than one month.

If your condition goes away and then comes back, your doctor may re-start the treatment.

Your doctor will decide on the schedule for follow up examinations.

If a dose of Eylea is missed
Make a new appointment for an examination and injection.

Stopping treatment with Eylea
Consult your doctor before stopping the treatment.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions (hypersensitivity) could potentially occur. **These may be serious and require that you contact your doctor immediately.**

With administration of Eylea, there may be some side effects affecting the eyes which are due to the injection procedure. Some of these may be **serious** and include **blindness**, **a serious infection or inflammation inside the eye** (endophthalmitis), **detachment, tear or bleeding of the light-sensitive layer at the back of the eye** (retinal detachment or tear), **clouding of the lens** (cataract), **bleeding in the eye** (vitreous haemorrhage), **detachment of the gel-like substance inside the eye from the retina** (vitreous detachment) and **increase of pressure inside the eye**, see section 2. These serious side effects affecting the eyes occurred in less than 1 in 1,900 injections in clinical studies.

If you experience a sudden decrease in vision, or an increase in pain and redness in your eye after your injection, **contact your doctor immediately**.

List of side effects reported
The following is a list of the side effects reported to be possibly related to the 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.

Very common side effects *(may affect more than 1 in 10 people):*
- deterioration of eyesight
- bleeding in the back of the eye (retinal haemorrhage)
- bloodshot eye caused by bleeding from small blood vessels in the outer layers of the eye
- eye pain

Common side effects *(may affect up to 1 in 10 people):*
- detachment or tear of one of the layers in the back of the eye, resulting in flashes of light with floaters sometimes progressing to a loss of vision (retinal pigment epithelial tear*/detachment, retinal detachment/tear)
- degeneration of the retina (causing disturbed vision)
- bleeding in the eye (vitreous haemorrhage)
- certain forms of clouding of the lens (cataract)
- damage to the front layer of the eyeball (the cornea)
- increase in eye pressure
- moving spots in vision (floaters)
- detachment of the gel-like substance inside the eye from the retina (vitreous detachment, resulting in flashes of light with floaters)
- a feeling of having something in the eye
- increased tear production
- swelling of the eyelid
- bleeding at the injection site
- redness of the eye

* Conditions known to be associated with wet AMD; observed in wet AMD patients only.

Uncommon side effects *(may affect up to 1 in 100 people):*
- allergic reactions (hypersensitivity)**
- serious inflammation or infection inside the eye (endophthalmitis)
- inflammation in the iris or other parts of the eye (iritis, uveitis, iridocyclitis, anterior chamber flare)
- abnormal sensation in the eye
- eyelid irritation
- swelling of the front layer of the eyeball (cornea)

** Allergic reactions like rash, itching (pruritus), hives (urticaria), and a few cases of severe allergy (anaphylactic/anaphylactoid) reactions were reported.

Rare side effects *(may affect up to 1 in 1,000 people):*
- blindness
- clouding of the lens due to injury (traumatic cataract)
- inflammation of the gel-like substance inside the eye
- pus in the eye

In the clinical trials, there was an increased incidence of bleeding from small blood vessels in the outer layers of the eye (conjunctival haemorrhage) in patients with wet AMD receiving blood thinners. This increased incidence was comparable between patients treated with ranibizumab and Eylea.

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

As with all therapeutic proteins, there is a possibility for an immune reaction (formation of antibodies) with Eylea.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via
België
Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten – www.fagg.be
Afdeling Vigilantie
Website: www.eenbijwerkingmelden.be
e-mail: adr@fagg.be

Luxemburg
Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé
Site internet : www.guichet.lu/pharmacovigilance

Nederland
Nederlands Bijwerkingen Centrum Lareb
Website: www.lareb.nl

By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Eylea

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C). Do not freeze.
- The unopened vial may be stored outside the refrigerator below 25°C for up to 24 hours.
- Store in the original package in order to protect from light.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away any medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Eylea contains
- The active substance is: aflibercept. One vial contains an extractable volume of at least 0.1 mL, equivalent to at least 4 mg aflibercept. One vial delivers a dose of 2 mg aflibercept in 0.05 mL.
- The other ingredients are: polysorbate 20 (E 432), sodium dihydrogen phosphate monohydrate (for pH adjustment), disodium hydrogen phosphate heptahydrate (for pH adjustment), sodium chloride, sucrose, water for injections.

What Eylea looks like and contents of the pack
Eylea is a solution for injection (injection) in a vial. The solution is colourless to pale yellow.
Pack size of 1 vial + 1 filter needle.

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
Germany

Manufacturer
Bayer AG
Müllerstraße 178
13353 Berlin
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Luxemburg	**Nederland**
Bayer SA-NV	Bayer B.V.
Tél/Tel: +32-(0)2-535 63 11	Tel: +31–(0)23-799 1000

This leaflet was last revised in 08/2024

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

The vial should only be used **for the treatment of a single eye.**

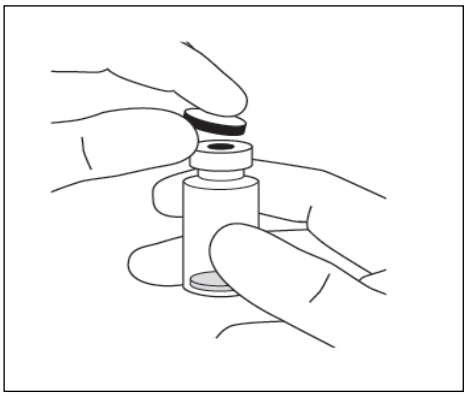
The vial contains more than the recommended dose of 2 mg aflibercept (equivalent to 0.05 mL). The excess volume must be discarded prior to administration.

The solution should be inspected visually for any foreign particulate matter and/or discolouration or any variation in physical appearance prior to administration. In the event of either being observed, discard the medicinal product.

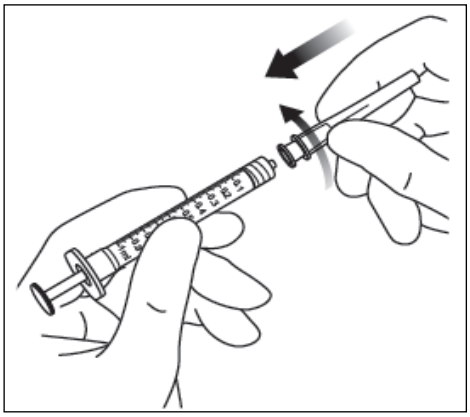
The unopened vial may be stored outside the refrigerator below 25° C for up to 24 hours. After opening the vial, proceed under aseptic conditions.
For the intravitreal injection, a 30 G x ½ inch injection needle should be used.

Instructions for use of vial:

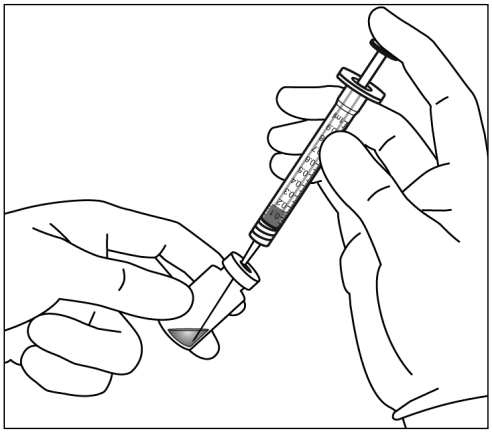
1. Remove the plastic cap and disinfect the outer part of the rubber stopper of the vial.

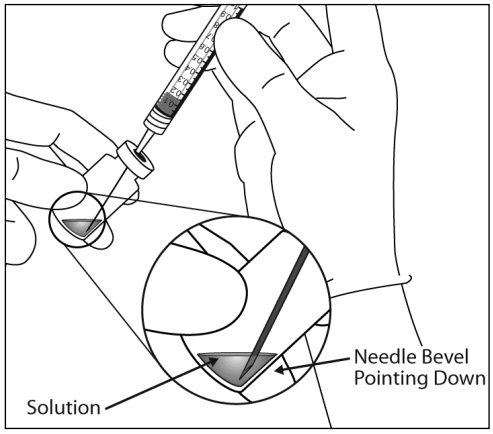


2. Attach the 18 G, 5-micron filter needle supplied in the carton to a 1 mL sterile Luer-lock syringe.



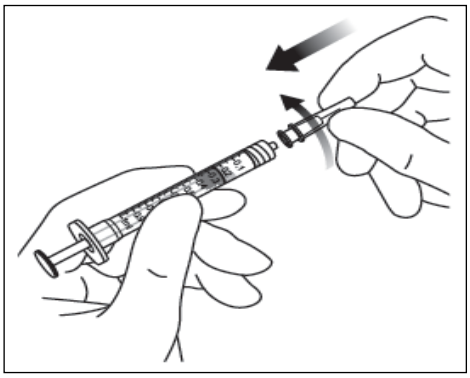
3. Push the filter needle into the centre of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.
4. Using aseptic technique withdraw all of the Eylea vial contents into the syringe, keeping the vial in an upright position, 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.



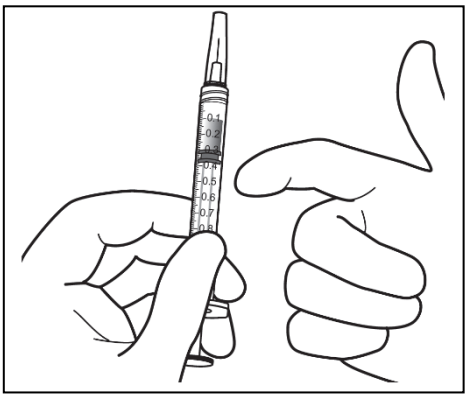


5. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.
6. Remove the filter needle and properly dispose of it.
   Note: Filter needle is not to be used for intravitreal injection.

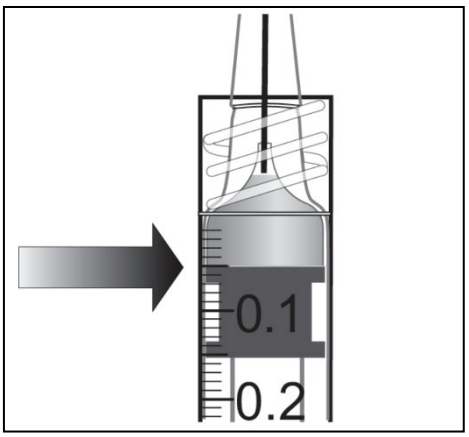
7. Using aseptic technique, firmly twist a 30 G x ½ inch injection needle onto the Luer-lock syringe tip.

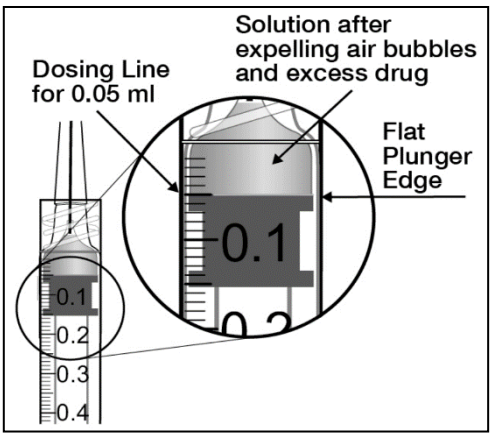


8. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



9. Eliminate all bubbles and expel excess medicinal product by slowly depressing the plunger so that the flat plunger edge aligns with the line that marks 0.05 mL on the syringe.





10. The vial is for single use only. Extraction of multiple doses from a single vial may increase the risk of contamination and subsequesnt infection.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the patient

Eylea 114.3 mg/ml solution for injection
aflibercept

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Eylea is and what it is used for

What Eylea is
Eylea contains the active substance aflibercept. It belongs to a group of medicines called antineovascularistion agents.

Your doctor will inject Eylea into your eye to treat eye disorders in adults called:
- wet age-related macular degeneration (wet AMD)
- visual impairment due to diabetic macular oedema (DME).

These disorders affect the macula. The macula is the central part of the light sensitive membrane at the back of the eye. It is responsible for clear vision.
Wet AMD is caused when abnormal blood vessels form and grow below the macula. The abnormal blood vessels may leak fluid or blood into the eye. Leaky blood vessels that cause swelling of the macula cause DME. Both disorders may impact your vision.

How Eylea works
Eylea stops growth of new abnormal blood vessels in the eye. Eylea can help to stabilise and often improve vision.

2. What you need to know before you receive Eylea

You will not receive Eylea if you
- are allergic to aflibercept or any of the other ingredients of this medicine (listed in section 6)
- have an infection in or around the eye
- have pain or redness in your eye (severe eye inflammation).

Warnings and precautions
Talk to your doctor **before receiving** Eylea if you:
- have glaucoma – an eye condition caused by high pressure in the eye
- have a history of seeing flashes of light or dark floating spots and if their size or number suddenly increases
- had eye surgery in the last 4 weeks or eye surgery is planned in the next 4 weeks.

Tell your doctor **immediately if** you develop:
- redness of the eye
- eye pain
- increased discomfort
- blurred or decreased vision
- increased sensitivity to light

These may be symptoms of an inflammation or infection and your doctor may stop giving you Eylea.

Furthermore, it is important for you to know that:
- the safety and efficacy of Eylea when administered to both eyes at the same time have not been studied and such use may increase risk of experiencing side effects.
- injections with Eylea may cause an increase in eye pressure in some patients within 60 minutes of the injection. Your doctor will monitor this after each injection.
- your doctor will check for other risk factors that may increase the chance of a tear or detachment of one of the layers at the back of the eye. In such cases your doctor will give you Eylea with caution.
- women who could become pregnant must use effective birth control during treatment and for at least 4 months after the last injection of Eylea.

The use of substances similar to those contained in Eylea is potentially related to the risk of blood clots blocking blood vessels, which may lead to heart attack or stroke. Theoretically, this could also happen after an injection of Eylea into the eye. If you had a stroke, a mini-stroke or a heart attack within the last 6 months, your doctor will give you Eylea with caution.

Children and adolescents
The use of Eylea in children or adolescents under 18 has not been studied because the diseases indicated occur mainly in adults. Therefore, its use in this age group is not relevant.

Other medicines and Eylea
Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding
- Women who could become pregnant must use effective birth control during treatment and for at least 4 months after the last injection of Eylea.
- There is limited experience on the use of Eylea in pregnant women. Women should not receive Eylea during pregnancy unless the potential benefit to the woman outweighs the potential risk to the unborn child.
- Small amounts of Eylea may pass into human milk. The effect on breast-fed newborns/infants are unknown. Eylea is not recommended during breast-feeding.

Therefore, if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you receive this medicine.

Driving and using machines
After receiving Eylea, you may experience some temporary vision problems. Do not drive or use machines as long as these last.

3. How Eylea will be given

The recommended dose is 8 mg aflibercept per injection.

- You will receive 1 injection every month for the first 3 months.
- After that, you may receive injections up to every 5 months. Your doctor will decide on the frequency based on the condition of your eye.

Method of administration
Your doctor will inject Eylea into your eye (intravitreal injection).

Before the injection, your doctor will use a disinfectant eyewash to clean your eye carefully to prevent infection. Your doctor will give you an eye drop (local anaesthetic) to numb the eye to reduce or prevent pain from the injection.

If you missed a dose of Eylea
Make a new appointment with your doctor as soon as possible.

Before stopping Eylea treatment
Speak with your doctor before stopping treatment. Stopping treatment may increase your risk of vision loss and your vision may worsen.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The side effects of Eylea injection are either from the medicine itself or from the injection procedure and mostly affect the eye.

Some side effects could be serious
Contact your doctor immediately if you have any of the following:
- common side effect, which may affect up to 1 in 10 people
  - clouding of the lens (cataract)
  - bleeding in the back of the eye (retinal haemorrhage)
  - increase of pressure inside the eye
  - bleeding inside the eye (vitreous haemorrhage)
- uncommon side effect, which may affect up to 1 in 100 people
  - certain forms of clouding of the lens (cataract subcapsular/nuclear)
  - detachment, tear or bleeding of the light-sensitive layer at the back of the eye, resulting in flashes of light with floaters, sometimes progressing to a loss of vision (retinal detachment or tear)

Other possible side effects
Common (may affect up to 1 in 10 people):
- allergic reactions
- moving spot in your vision (vitreous floaters)
- detachment of the gel-like substance inside the eye (vitreous detachment)
- reduced sharpness of vision
- eye pain
- bleeding inside the eye (conjunctival haemorrhage)
- damage to the clear layer of the eyeball in front of the iris (punctate keratitis, corneal abrasion)

Uncommon (may affect up to 1 in 100 people):
- detachment or tear of one of the layers in the back of the eye, resulting in flashes of light with floaters, sometimes progressing to a loss of vision (retinal pigment epithelial tear/detachment)
- inflammation in the iris, of other parts of the eye, or the gel-like substance inside the eye (uveitis, iritis, iridocyclitis, vitritis)
- certain forms of clouding of the lens (cataract cortical)
- damage to the front layer of the eyeball (corneal erosion)
- blurred vision
- eye pain at injection site
- a feeling of having something in the eye
- increased tear production
- bleeding at the injection site
- redness of the eye
- swelling of the eyelid
- redness of the eye (ocular hyperaemia)
- irritation at injection site

Rare (may affect up to 1 in 1 000 people):
- swelling of the front layer of the eyeball (corneal oedema)
- clouding of the lens (lenticular opacities)
- degeneration of the light sensitive membrane at the back of the eye (retinal degeneration)
- eyelid irritation

Besides the above the following side effects may occur although they have not been reported in clinical studies:
- abnormal sensation in eye
- damage to the surface of the clear front layer of the eye (corneal epithelium defect)
- inflammation of other parts of the eye (anterior chamber flare)
- serious inflammation or infection inside the eye (endophthalmitis)
- blindness
- clouding of the lens due to injury (traumatic cataract)
- pus in the eye (hypopyon)
- severe allergic reactions

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via
België
Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten – www.fagg.be
Afdeling Vigilantie
Website: www.eenbijwerkingmelden.be
e-mail: adr@fagg.be

Luxemburg
Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé
Site internet : www.guichet.lu/pharmacovigilance

Nederland
Nederlands Bijwerkingen Centrum Lareb
Website: www.lareb.nl

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Eylea

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2 °C – 8 °C). Do not freeze.
- The unopened vial may be stored outside the refrigerator below 25 °C for up to 24 hours.
- Keep the vial in the outer carton in order to protect from light.

6. Contents of the pack and other information

What Eylea contains
- The active substance is aflibercept. 1 ml solution contains 114.3 mg aflibercept. Each vial contains 0.263 ml. This provides a usable amount to deliver a single dose of 0.07 ml containing 8 mg aflibercept.
- The other ingredients are: sucrose, arginine hydrochloride, histidine hydrochloride monohydrate, histidine, polysorbate 20, water for injections.

What Eylea looks like and contents of the pack
Eylea is a solution for injection (injection). The solution is colourless to pale yellow.
Pack size: 1 vial + 1 filter needle.

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
Germany

Manufacturer
Bayer AG
Müllerstraße 178
13353 Berlin
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Luxemburg	**Nederland**
Bayer SA-NV	Bayer B.V.
Tél/Tel: +32-(0)2-535 63 11	Tel: +31–(0)23-799 1000

This leaflet was last revised in 08/2024

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

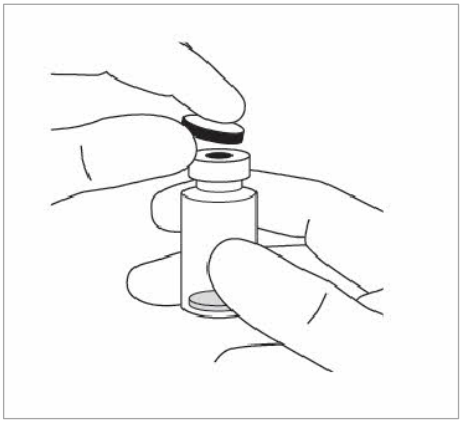
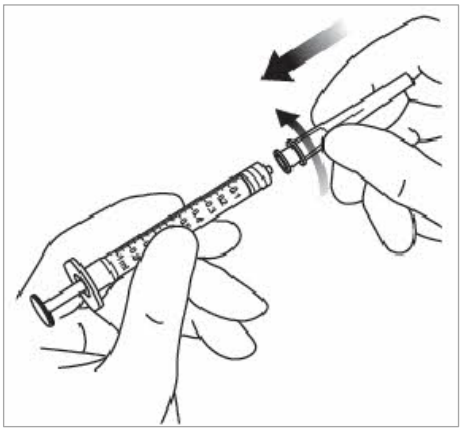
The following information is intended for healthcare professionals only:

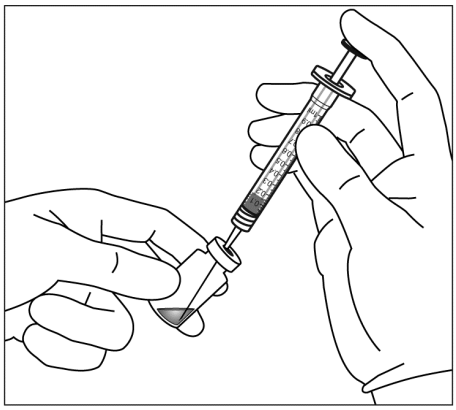
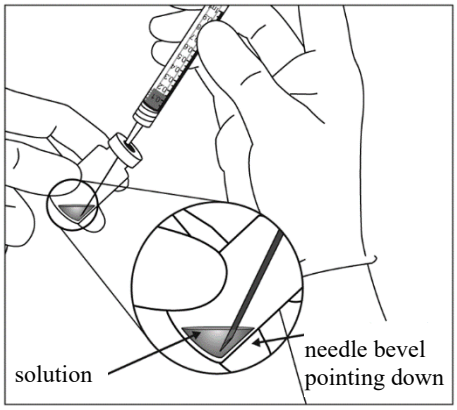
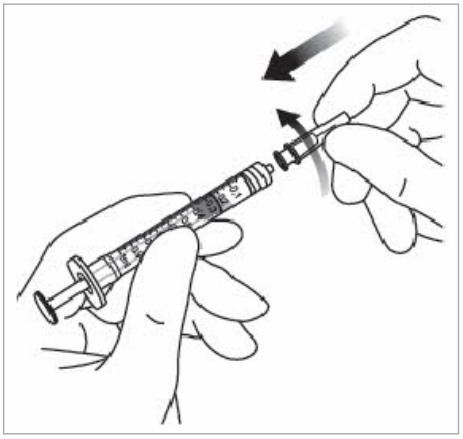
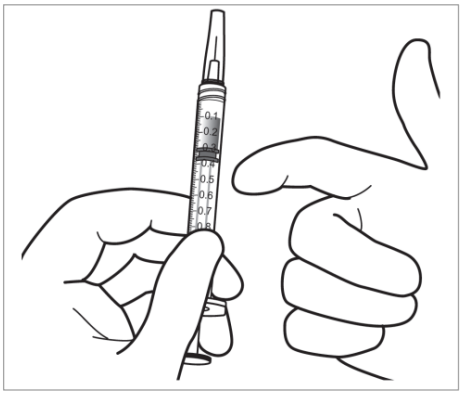
The vial is for single use in one eye only. Extraction of multiple doses from a single vial may increase the risk of contamination and subsequent infection.

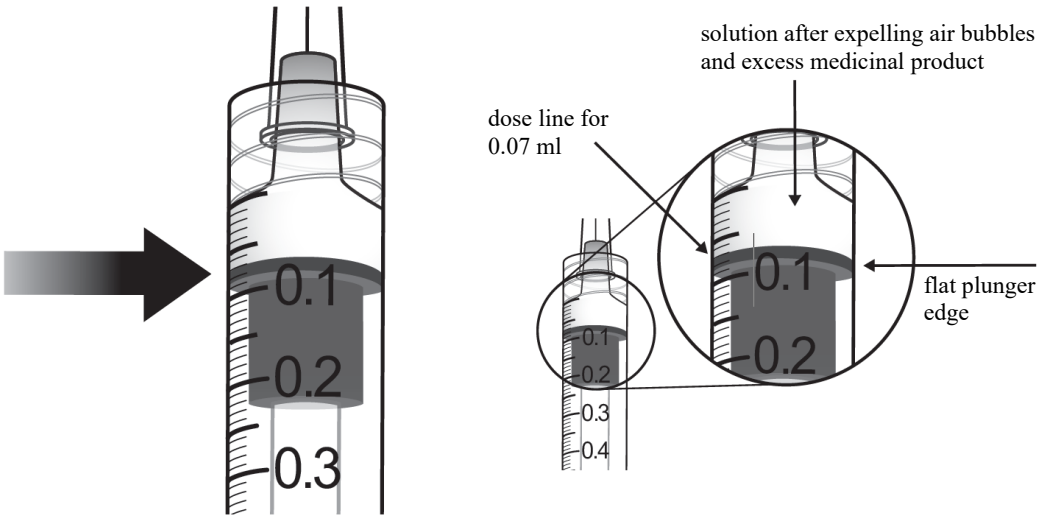
Do not use if the package or its components are expired, damaged, or have been tampered with.

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.

The intravitreal injection should be performed with a 30 G × ½ inch injection needle (not included). Use of a smaller size needle (higher gauge) than the recommended 30 G × ½ inch injection needle may result in increased injection forces.

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.

Package leaflet: Information for the patient

Eylea 114.3 mg/ml solution for injection in pre-filled syringe
aflibercept

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Eylea is and what it is used for

What Eylea is
Eylea contains the active substance aflibercept. It belongs to a group of medicines called antineovascularistion agents.

Your doctor will inject Eylea into your eye to treat eye disorders in adults called:
- wet age-related macular degeneration (wet AMD)
- visual impairment due to diabetic macular oedema (DME).

These disorders affect the macula. The macula is the central part of the light sensitive membrane at the back of the eye. It is responsible for clear vision.
Wet AMD is caused when abnormal blood vessels form and grow below the macula. The abnormal blood vessels may leak fluid or blood into the eye. Leaky blood vessels that cause swelling of the macula cause DME. Both disorders may impact your vision.

How Eylea works
Eylea stops growth of new abnormal blood vessels in the eye. Eylea can help to stabilise and often improve vision.

2. What you need to know before you receive Eylea

You will not receive Eylea if you
- are allergic to aflibercept or any of the other ingredients of this medicine (listed in section 6)
- have an infection in or around the eye
- have pain or redness in your eye (severe eye inflammation).

Warnings and precautions
Talk to your doctor **before receiving** Eylea if you:
- have glaucoma – an eye condition caused by high pressure in the eye
- have a history of seeing flashes of light or dark floating spots and if their size or number suddenly increases
- had eye surgery in the last 4 weeks or eye surgery is planned in the next 4 weeks.

Tell your doctor **immediately if** you develop:
- redness of the eye
- eye pain
- increased discomfort
- blurred or decreased vision
- increased sensitivity to light

These may be symptoms of an inflammation or infection and your doctor may stop giving you Eylea.

Furthermore, it is important for you to know that:
- the safety and efficacy of Eylea when administered to both eyes at the same time have not been studied and such use may increase risk of experiencing side effects.
- injections with Eylea may cause an increase in eye pressure in some patients within 60 minutes of the injection. Your doctor will monitor this after each injection.
- your doctor will check for other risk factors that may increase the chance of a tear or detachment of one of the layers at the back of the eye. In such cases your doctor will give you Eylea with caution.
- women who could become pregnant must use effective birth control during treatment and for at least 4 months after the last injection of Eylea.

The use of substances similar to those contained in Eylea is potentially related to the risk of blood clots blocking blood vessels, which may lead to heart attack or stroke. Theoretically, this could also happen after an injection of Eylea into the eye. If you had a stroke, a mini-stroke or a heart attack within the last 6 months, your doctor will give you Eylea with caution.

Children and adolescents
The use of Eylea in children or adolescents under 18 has not been studied because the diseases indicated occur mainly in adults. Therefore, its use in this age group is not relevant.

Other medicines and Eylea
Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding
- Women who could become pregnant must use effective birth control during treatment and for at least 4 months after the last injection of Eylea.
- There is limited experience on the use of Eylea in pregnant women. Women should not receive Eylea during pregnancy unless the potential benefit to the woman outweighs the potential risk to the unborn child.
- Small amounts of Eylea may pass into human milk. The effect on breast-fed newborns/infants are unknown. Eylea is not recommended during breast-feeding.

Therefore, if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you receive this medicine.

Driving and using machines
After receiving Eylea, you may experience some temporary vision problems. Do not drive or use machines as long as these last.

3. How Eylea will be given

The recommended dose is 8 mg aflibercept per injection.

- You will receive 1 injection every month for the first 3 months.
- After that, you may receive injections up to every 5 months. Your doctor will decide on the frequency based on the condition of your eye.

Method of administration
Your doctor will inject Eylea into your eye (intravitreal injection).

Before the injection, your doctor will use a disinfectant eyewash to clean your eye carefully to prevent infection. Your doctor will give you an eye drop (local anaesthetic) to numb the eye to reduce or prevent pain from the injection.

If you missed a dose of Eylea
Make a new appointment with your doctor as soon as possible.

Before stopping Eylea treatment
Speak with your doctor before stopping treatment. Stopping treatment may increase your risk of vision loss and your vision may worsen.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The side effects of Eylea injection are either from the medicine itself or from the injection procedure and mostly affect the eye.

Some side effects could be serious
Contact your doctor immediately if you have any of the following:
- common side effect, which may affect up to 1 in 10 people
  - clouding of the lens (cataract)
  - bleeding in the back of the eye (retinal haemorrhage)
  - increase of pressure inside the eye
  - bleeding inside the eye (vitreous haemorrhage)
- uncommon side effect, which may affect up to 1 in 100 people
  - certain forms of clouding of the lens (cataract subcapsular/nuclear)
  - detachment, tear or bleeding of the light-sensitive layer at the back of the eye, resulting in flashes of light with floaters, sometimes progressing to a loss of vision (retinal detachment or tear)

Other possible side effects
Common (may affect up to 1 in 10 people):
- allergic reactions
- moving spot in your vision (vitreous floaters)
- detachment of the gel-like substance inside the eye (vitreous detachment)
- reduced sharpness of vision
- eye pain
- bleeding inside the eye (conjunctival haemorrhage)
- damage to the clear layer of the eyeball in front of the iris (punctate keratitis, corneal abrasion)

Uncommon (may affect up to 1 in 100 people):
- detachment or tear of one of the layers in the back of the eye, resulting in flashes of light with floaters, sometimes progressing to a loss of vision (retinal pigment epithelial tear/detachment)
- inflammation in the iris, of other parts of the eye, or the gel-like substance inside the eye (uveitis, iritis, iridocyclitis, vitritis)
- certain forms of clouding of the lens (cataract cortical)
- damage to the front layer of the eyeball (corneal erosion)
- blurred vision
- eye pain at injection site
- a feeling of having something in the eye
- increased tear production
- bleeding at the injection site
- redness of the eye
- swelling of the eyelid
- redness of the eye (ocular hyperaemia)
- irritation at injection site

Rare (may affect up to 1 in 1 000 people):
- swelling of the front layer of the eyeball (corneal oedema)
- clouding of the lens (lenticular opacities)
- degeneration of the light sensitive membrane at the back of the eye (retinal degeneration)
- eyelid irritation

Besides the above the following side effects may occur although they have not been reported in clinical studies:
- abnormal sensation in eye
- damage to the surface of the clear front layer of the eye (corneal epithelium defect)
- inflammation of other parts of the eye (anterior chamber flare)
- serious inflammation or infection inside the eye (endophthalmitis)
- blindness
- clouding of the lens due to injury (traumatic cataract)
- pus in the eye (hypopyon)
- severe allergic reactions

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via

België
Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten – www.fagg.be
Afdeling Vigilantie
Website: www.eenbijwerkingmelden.be
e-mail: adr@fagg.be

Luxemburg
Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé
Site internet : www.guichet.lu/pharmacovigilance

Nederland
Nederlands Bijwerkingen Centrum Lareb
Website: www.lareb.nl

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Eylea

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2 °C – 8 °C). Do not freeze.
- Keep the pre-filled syringe in its blister and in the outer carton in order to protect from light.
- Prior to usage, the unopened blister may be stored outside the refrigerator below 25 °C for up to 24 hours.

6. Contents of the pack and other information

What Eylea contains
- The active substance is aflibercept. 1 ml solution contains 114.3 mg aflibercept. Each pre-filled syringe contains 0.184 ml. This provides a usable amount to deliver a single dose of 0.07 ml containing 8 mg aflibercept.
- The other ingredients are: sucrose, arginine hydrochloride, histidine hydrochloride monohydrate, histidine, polysorbate 20, water for injections.

What Eylea looks like and contents of the pack
Eylea 114.3 mg/ml solution for injection in pre-filled syringe is a solution for injection (injection). The solution is colourless to pale yellow.
Pack size: 1 pre-filled syringe.

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
Germany

Manufacturer
Bayer AG
Müllerstraße 178
13353 Berlin
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Luxemburg	**Nederland**
Bayer SA-NV	Bayer B.V.
Tél/Tel: +32-(0)2-535 63 11	Tel: +31–(0)23-799 1000

This leaflet was last revised in 08/2024

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

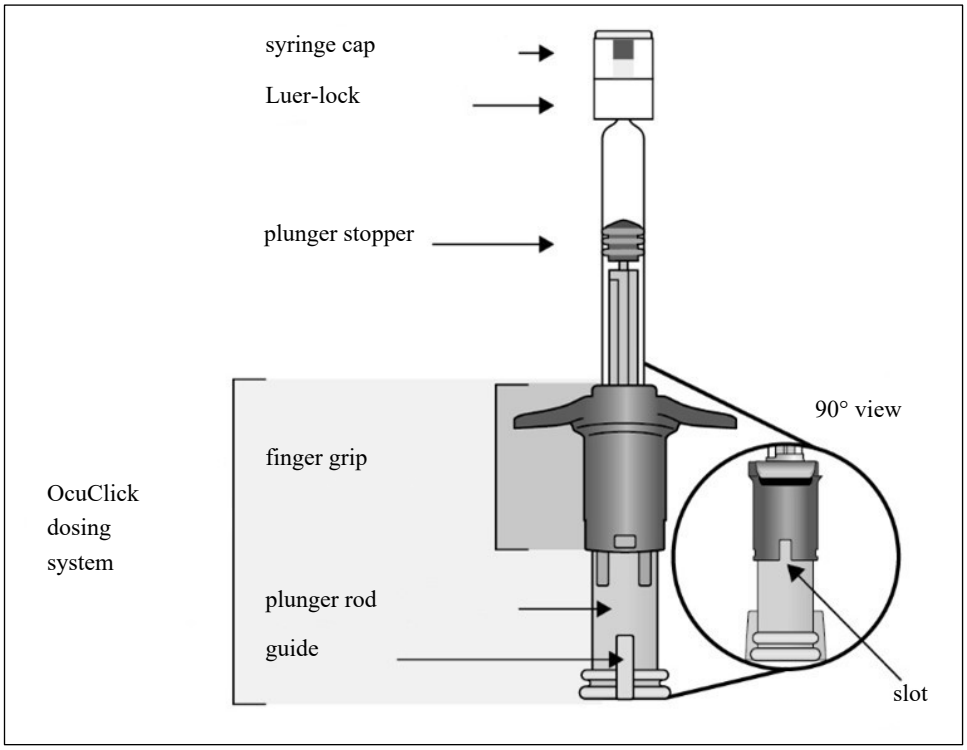
The following information is intended for healthcare professionals only:

The pre-filled syringe with OcuClick dosing system is for single use in one eye only. Extraction of multiple doses from a single pre-filled syringe with OcuClick dosing system may increase the risk of contamination and subsequent infection.

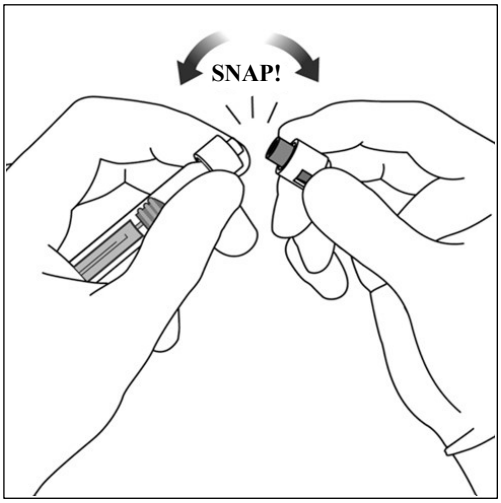
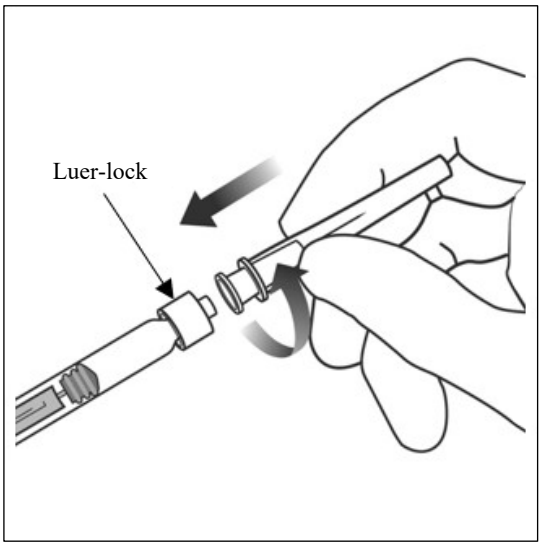
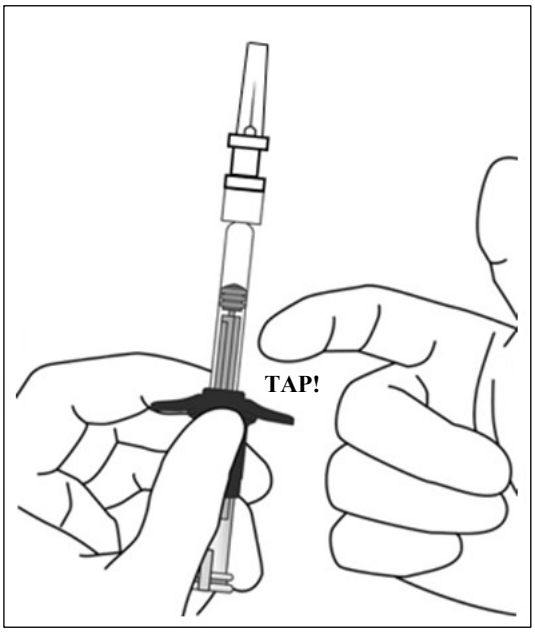
Do not use if the package or its components are expired, damaged, or have been tampered with. Check the label on the pre-filled syringe with OcuClick dosing system to make sure you have the strength of Eylea that you intended to use. The 8 mg dose requires use of the Eylea 114.3 mg/ml pre-filled syringe.

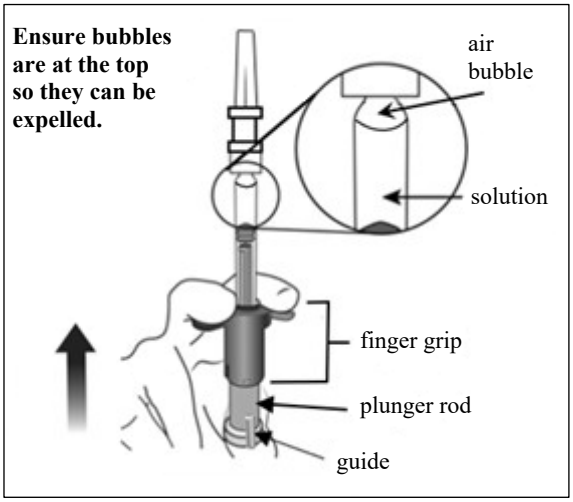
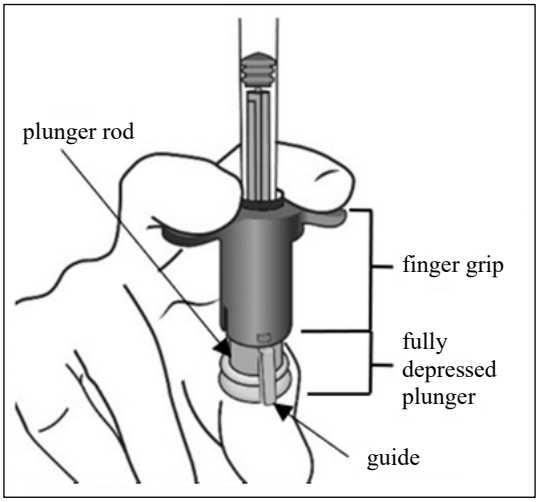
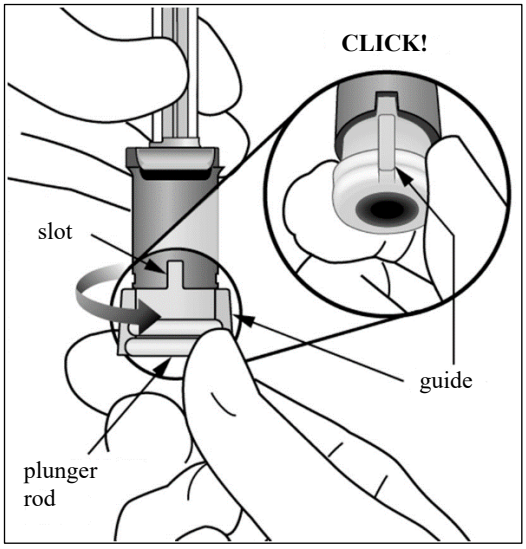
The intravitreal injection should be performed with a 30 G × ½ inch injection needle (not included). Use of a smaller size needle (higher gauge) than the recommended 30 G × ½ inch injection needle may result in increased injection forces.

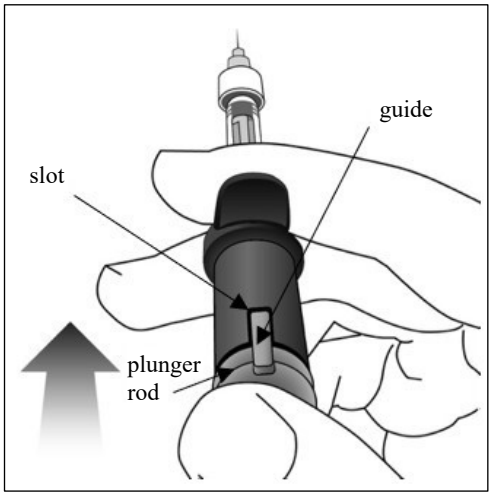
Pre-filled syringe with integrated OcuClick dosing system description



1.	Prepare When ready to administer Eylea 114.3mg/ml, open the carton and remove the sterile blister. Carefully peel open the blister ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready to attach the injection needle. Use aseptic technique to carry out steps 2-9.
2.	Remove syringe Remove the syringe from the sterilised blister.
3.	Inspect syringe and solution for injection **Do not** use the pre-filled syringe if - particulates, cloudiness, or discolouration are visible - any part of the pre-filled syringe with OcuClick dosing system is damaged or loose - the syringe cap is detached from the Luer-lock.

4.	Snap off syringe cap To **snap off** (do not twist off) the syringe cap, hold the syringe in one hand and the syringe cap with the thumb and forefinger of the other hand. **Note:** Do not pull back on the plunger rod. 
5.	Attach needle Firmly twist the 30 G × ½ inch injection needle onto the Luer-lock syringe tip. 
6.	Dislodge air bubbles 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. 

7.	Expel air and excess volume to prime The syringe does not have a dose line because it is designed to set the dose mechanically as explained in the steps below. Priming and setting the dose must be done using the following steps. To eliminate all bubbles and to expel excess medicinal product, slowly depress the plunger rod (left picture below) until it stops, i.e. when the guide on the plunger rod reaches the finger grip (right picture below).  
8.	Set the dose Turn the end of the plunger rod 90 degrees clockwise or counter clockwise until the guide of the plunger rod aligns with the slot. You may hear a 'click'. **Note:** Now the device is ready to dose. Do not push the plunger rod before insertion into the eye. 

9.	Administer the injection Insert the needle into the ocular injection site. Inject the solution by pushing in the plunger rod until it stops, i.e. until the guide is completely within the slot. Do not apply additional pressure once the guide is within the slot. It is normal to see a small amount of residual solution left in the syringe. 
10.	The pre-filled syringe is for single dose administration and single use only. After injection discard the used syringe into a sharps container.

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