The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it in March 2014

Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

Eylea 40 mg/ml solution for injection in a vial.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 40 mg aflibercept*.

Each vial contains 100 microlitres, equivalent to 4 mg aflibercept. This provides a usable amount to deliver a single dose of 50 microlitres containing 2 mg aflibercept.

*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 intravitreal injection .

The solution is a clear, colourless to pale yellow and iso-osmotic solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Eylea is indicated for adults for the treatment of

- neovascular (wet) age-related macular degeneration (AMD) (see section 5.1).
- visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO) (see section 5.1).

4.2 Posology and method of administration

Eylea is for intravitreal injection only.

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

Posology

wet AMD

The recommended dose for Eylea is 2 mg aflibercept, equivalent to 50 microlitres.

Eylea treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections.

After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections.

Macular Oedema secondary to CRVO

The recommended dose for Eylea is 2 mg aflibercept equivalent to 50 microlitres.

After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month.

If there is no improvement in visual and anatomic outcomes over the course of the first three injections, continued treatment is not recommended.

Monthly treatment continues until visual and anatomic outcomes are stable for three monthly assessments. Thereafter the need for continued treatment should be reconsidered.

If necessary, treatment may be continued with gradually increasing treatment intervals to maintain a stable visual and anatomic outcome. If treatment has been discontinued, visual and anatomic outcomes should be monitored and treatment should be resumed if these deteriorate.

Usually, monitoring should be done at the injection visits. During treatment interval extension through to completion of therapy, the monitoring schedule should be determined by the treating physician based on the individual patient's response and may be more frequent than the schedule of injections.

Special populations

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

Available data do not suggest a need for a dose adjustment with Eylea in these patients (see section 5.2).

Elderly population
No special considerations are needed.

Paediatric population
Safety and efficacy have not been established in children and adolescents. There is no relevant use of Eylea in the paediatric population in the indications wet AMD and CRVO.

Method of administration

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 3.5-4.0 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 0.05 ml is then delivered; a different scleral site should be used for subsequent injections.

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

Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay.

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

The vial contains more than the recommended dose of 2 mg aflibercept. The extractable volume of the vial (100 microlitres) is not to be used in total. The excess volume should be expelled before injecting. Injecting the entire volume could result in overdose. To expel the air bubble along with excess medicinal product, slowly depress the plunger to align the cylindrical base of the dome plunger with the black dosing line on the syringe (equivalent to 50 microlitres i.e. 2 mg aflibercept).

After injection any unused product must be discarded.

For handling of the medicinal product, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Endophthalmitis
Intravitreal injections, including those with aflibercept, have been associated with endophthalmitis (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 without delay, and these should be managed appropriately.

Increase in intraocular pressure
Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with Eylea (see section 4.8). Special precaution is needed in patients with poorly controlled glaucoma (do not inject Eylea while the intraocular pressure is $\geq$ 30 mmHg). In all cases, both the intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately.

Immunogenicity
As this is a therapeutic protein, there is a potential for immunogenicity with Eylea (see section 4.8). 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.

Other
As with other intravitreal anti-VEGF treatments for AMD and CRVO the following also applies:

- The safety and efficacy of Eylea therapy administered to both eyes concurrently have not been systematically studied.
- Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD, include a large and/or high pigment epithelial retinal detachment. When initiating Eylea therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.
- Treatment should be withheld in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes.
- In the event of a retinal break the dose should be withheld and treatment should not be resumed until the break is adequately repaired**.**
- The dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of:
    - a decrease in best-corrected visual acuity (BCVA) of ≥30 letters compared with the last assessment of visual acuity;
    - a subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥50%, of the total lesion area.
- The dose should be withheld within the previous or next 28 days in the event of a performed or planned intraocular surgery.
- Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus (see section 4.6).
- Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept (see section 4.6).
- There is limited experience with treatment of patients with ischemic, chronic CRVO. In patients presenting with clinical signs of irreversible ischemic visual function loss, the treatment is not recommended.
- There is limited clinical data with Eylea in patients with diabetic retinopathy.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Adjunctive use of verteporfin photodynamic therapy (PDT) and Eylea has not been studied, therefore, a safety profile is not established.

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 3 months after the last intravitreal injection of aflibercept (see section 4.4).

Pregnancy
There are no data on the use of aflibercept in pregnant women.
Studies in animals have shown embryo-foetal toxicity (see section 5.3).

Although the systemic exposure after ocular administration is very low, Eylea should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.

Breastfeeding
It is unknown whether aflibercept is excreted in human milk. A risk to the breast-fed child cannot be excluded.

Eylea is not recommended during breastfeeding. A decision must be made whether to discontinue breastfeeding or to abstain from Eylea therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
Results from animal studies with high systemic exposure indicate that aflibercept can impair male and female fertility (see section 5.3). Such effects are not expected after ocular administration with very low systemic exposure.

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 disturbances associated either with the injection or the 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

wet AMD
A total of 1,824 patients constituted the safety population in the two phase 3 studies with up to 96 weeks of exposure to Eylea, of which 1,223 patients were treated with the 2 mg dose.

Serious adverse reactions related to the injection procedure have occurred in less than 1 in 1,000 intravitreal injections with Eylea and included endophthalmitis, traumatic cataract and transient increased intraocular pressure (see section 4.4).

The most common adverse reactions (in at least 5% of patients treated with Eylea) were conjunctival haemorrhage (26.7%), eye pain (10.3%), vitreous detachment (8.4%), cataract (7.9%), vitreous floaters (7.6%) and increased intraocular pressure (7.2%).

Macular Oedema secondary to CRVO

A total of 317 patients treated with at least one dose of Eylea constituted the safety population in the two phase III studies with up to 100 weeks exposure.

Serious adverse reactions related to the injection procedure occurred in 3 out of 2,728 intravitreal injections with Eylea and included endophthalmitis (see section 4.4), cataract and vitreous detachment.

The most common adverse reactions (in at least 5% of patients treated with Eylea) were conjunctival haemorrhage (15.8%), increased intraocular pressure (12.9%), eye pain (12.6%), vitreous detachment (6.9%), vitreous floaters (5.7%), increased lacrimation (5.0%) and ocular hyperemia (5.0%).

Tabulated list of adverse reactions

The safety data described below include all adverse reactions from the wet AMD and/or CRVO phase III studies with a reasonable possibility of causality to the injection procedure or medicinal product.

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)

Table 1: Adverse drug reactions reported in the wet AMD and CRVO phase III studies

System Organ Class	Very common	Common	Uncommon	Rare
Immune system disorders			Hypersensitivity***	
Eye disorders	Conjunctival haemorrhage, Eye pain	Retinal pigment epithelium tear*, Detachment of the retinal pigment epithelium*, Retinal degeneration, Vitreous haemorrhage, Cataract, Cataract nuclear, Cataract subcapsular, Corneal erosion, Corneal abrasion, Intraocular pressure increased, Vision blurred, Vitreous floaters, Corneal oedema, Vitreous detachment, Injection site pain, Foreign body sensation in eyes, Lacrimation increased, Eyelid oedema, Injection site haemorrhage, Conjunctival hyperaemia, Ocular hyperaemia	Endophthalmitis**, Retinal detachment, Retinal tear, Iritis, Iridocyclitis, Cataract cortical, Lenticular opacities, Corneal epithelium defect, Injection site irritation, Abnormal sensation in eye, Eyelid irritation Anterior chamber flare	Vitritis Uveitis, Hypopyon

* Conditions known to be associated with wet AMD. Observed in the wet AMD studies only.

** Culture positive and culture negative endophthalmitis

*** including allergic reactions

Description of selected adverse reactions

In the wet AMD phase III studies, there was an increased incidence of conjunctival haemorrhage in patients receiving anti-thrombotic agents. This increased incidence was comparable between patients treated with ranibizumab and Eylea.
Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.

ATEs, as defined by Antiplatelet Trialists' Collaboration (APTC) criteria, include nonfatal myocardial infarction, nonfatal stroke, or vascular death (including deaths of unknown cause). The incidence in the phase 3 wet AMD studies (VIEW1 and VIEW2) during the 96 weeks study duration was 3.3% (60 out of 1,824) in the combined group of patients treated with Eylea compared with 3.2% (19 out of 595) in patients treated with ranibizumab (see section 5.1).

The incidence of ATEs in the CRVO studies (GALILEO and COPERNICUS) during the 76/100 weeks study duration was 0.6% (2 out of 317) in patients treated with at least one dose of Eylea compared to 1.4% (2 out of 142) in the group of patients receiving only sham treatment.

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

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 .

4.9 Overdose

In clinical trials, doses of up to 4 mg in monthly intervals have been used and isolated cases of overdoses with 8 mg occurred.

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.

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.

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.

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 synergize with VEGF-A in these processes, and is also known to promote leucocyte infiltration and vascular inflammation.

Pharmacodynamic effects

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

In patients treated with Eylea (one injection per month for three consecutive months, followed by one injection every 2 months), retinal thickness decreased soon after treatment initiation, and the mean CNV lesion size was reduced, consistent with the results seen with ranibizumab 0.5 mg every month.

In the VIEW1 study there were mean decreases in retinal thickness on optical coherence tomography (OCT) (-130 and -129 microns at week 52 for the Eylea 2 mg every two months and ranibizumab 0.5 mg every month study groups, respectively). Also at the 52 week time point, in the VIEW2 study there were mean decreases in retinal thickness on OCT (-149 and -139 microns for the Eylea 2 mg every two months and ranibizumab 0.5 mg every month study groups, respectively).

The reduction of CNV size and reduction in retinal thickness were generally maintained in the second year of the studies.

Macular Oedema secondary to CRVO

In CRVO retinal ischaemia occurs and signals the release of VEGF which in turn destabilises the tight junctions and promotes endothelial cell proliferation. Up-regulation of VEGF is associated with the breakdown of the blood retina barrier and this increased vascular permeability results in retinal oedema, stimulation of endothelial cell growth and neovascularisation.

In patients treated with Eylea (one injection every month for six months) there was consistent, rapid and robust response in morphology (central retinal thickness [CRT] as assessed by OCT). Improvements in mean CRT were maintained through week 24.

Retinal thickness on OCT at week 24 compared to baseline was a secondary efficacy variable in both COPERNICUS and GALILEO study. In both studies, the mean change in retinal thickness from baseline to week 24 was statistically significant favouring Eylea.

Table 2: Pharmacodynamic parameter at week 24, week 52 and week 76/100 (Full Analysis Set with LOCF) in COPERNICUS and GALILEO studies

Efficacy Outcomes	COPERNICUS						GALILEO					
	24 Weeks		52 Weeks		100 Weeks		24 Weeks		52 Weeks		76 Weeks	
	Control (n = 73)	Eylea 2 mg Q4 (n = 114)	Control[C)] (n = 73)	Eylea 2 mg (n = 114)	Control [C,D)] (n = 65)	Eylea[D)] 2 mg (n = 112)	Control (n = 67)	Eylea 2 mg Q4 (n = 103)	Control (n = 67)	Eylea 2 mg (n = 103)	Control [E)] (n = 67)	Eylea [E)] 2 mg (n = 103)
Mean change in retinal thickness from baseline	-145	-457	-382	-413	-343	-390	-169	-449	-219	-424	-306	-389
Difference in LS mean[A,B,C)] (95% CI) p-value		-312 (-389, -234) p < 0.0001		-28 (-121, 64) p = 0.5460		-45 (-142, 53) p=0.3661		-239 (-286, -193) p < 0.0001		-167 (-217, -118) p < 0.0001		-44 (-99, 10) p=0.1122

A) Difference is Eylea 2 mg Q4 minus control

B) LS: Least square mean difference and confidence interval (CI) based on an ANCOVA model with baseline value as covariate and factors treatment group, region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)

C) In COPERNICUS study, control group patients could receive Eylea on an as-needed basis as frequently as every 4 weeks during week 24 to week 52

D) In COPERNICUS study, both control group and Eylea 2mg patients received Eylea 2 mg on an as-needed basis as frequently as every 4 weeks starting from Week 52 to Week 88

E) In GALILEO study, both control group and Eylea 2mg patients received Eylea 2 mg on an as-needed basis every 8 weeks starting from Week 52 to Week 68.

Clinical efficacy and safety

wet AMD
The safety and efficacy of Eylea were assessed in two randomised, multi-centre, double-masked, active-controlled studies in patients with wet AMD. A total of 2,412 patients were treated and evaluable for efficacy (1,817 with Eylea) in the two studies (VIEW1 and VIEW2). In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:

1) Eylea administered at 2 mg every 8 weeks following 3 initial monthly doses (Eylea 2Q8);
2) Eylea administered at 2 mg every 4 weeks (Eylea 2Q4);
3) Eylea administered at 0.5 mg every 4 weeks (Eylea 0.5Q4); and
4) ranibizumab administered at 0.5 mg every 4 weeks (ranibizumab 0.5Q4).

Patient ages ranged from 49 to 99 years with a mean of 76 years.

In the second year of the studies, patients continued to receive the dosage strength to which they were initially randomised but on a modified dosing schedule guided by assessment of visual and anatomic outcomes with a protocol-defined maximum dosing interval of 12 weeks.

In both studies, the primary efficacy endpoint was the proportion of patients in the Per Protocol Set who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline.

In the VIEW1 study, at week 52, 95.1% of patients in the Eylea 2Q8 treatment group maintained vision compared to 94.4% patients in the ranibizumab 0.5Q4 group. Eylea treatment was shown to be non-inferior and clinically equivalent to the ranibizumab 0.5Q4 group.

In the VIEW2 study, at week 52, 95.6% of patients in the Eylea 2Q8 treatment group maintained vision compared to 94.4% patients in the ranibizumab 0.5Q4 group. Eylea treatment was shown to be non-inferior and clinically equivalent to the ranibizumab 0.5Q4 group.

Detailed results from the combined analysis of both studies are shown in the Table and Figure below.

Table 3: Efficacy outcomes at week 52 (primary analysis) and week 96; combined data from the VIEW1 and VIEW2 studies[B)]

Efficacy Outcome	**Eylea 2Q8** [E)] (Eylea 2 mg every 8 weeks following 3 initial monthly doses) **(n = 607)**		**Ranibizumab 0.5Q4** (ranibizumab 0.5 mg every 4 weeks) **(n = 595)**	
	Week 52	Week 96 [G)]	Week 52	Week 96 [G)]
Mean number of injections from baseline	7.6	11.2	12.3	16.5
Mean number of injections during second year (Week 52 to 96)		4.2		4.7
Proportion of patients with maintained visual acuity (< 15 letters of BCVA[A)] loss) (Per Protocol Set)	95.33%[B)]	92.42%	94.42% [B)]	91.60%
Difference[C)] (95% CI)[D)]	0.9% (-1.7, 3.5)[F)]	0.8% (-2.3, 3.8)[F)]		
Mean change in BCVA as measured by ETDRS[A)] letter score from baseline	8.40	7.62	8.74	7.89
Difference in LS [A)] mean change (ETDRS letters)[C)] (95% CI)[D)]	-0.32 (-1.87, 1.23)	-0.25 (-1.98, 1.49)		
Proportion of patients who gained at least 15 letters of vision from baseline	30.97%	33.44%	32.44%	31.60%
Difference[C)] (95% CI)[D)]	-1.5% (-6.8, 3.8)	1.8% (-3.5, 7.1)		

[A)] BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LS: Least square means derived from ANCOVA

[B)] Full Analysis Set (FAS), Last Observation Carried Forward (LOCF) for all analyses except proportion of patients with maintained visual acuity at week 52 which is Per Protocol Set (PPS)

[C)] The difference is the value of the Eylea group minus the value of the ranibizumab group. A positive value favours Eylea.

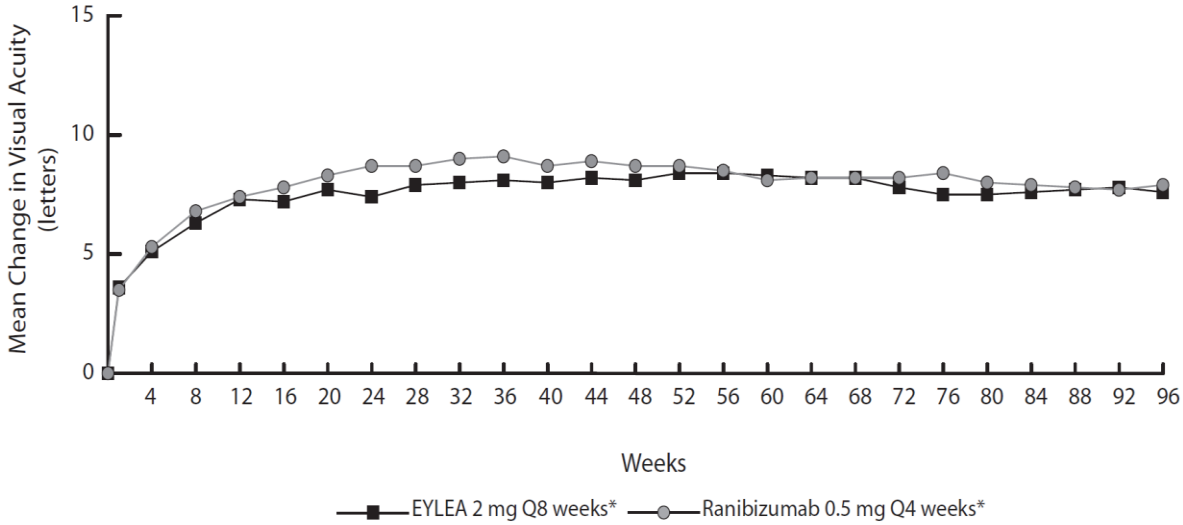
[D)] Confidence interval (CI) calculated by normal approximation

[E)] After treatment initiation with three monthly doses

[F)] A confidence interval lying entirely above -10% indicates a non-inferiority of Eylea to ranibizumab

[G)] Beginning at week 52, all groups were treated using a modified quarterly treatment paradigm where patients could be dosed as frequently as every 4 weeks but not less frequently than every 12 weeks based upon pre-specified retreatment criteria

Figure 1. Mean Change in Visual Acuity
from Baseline to Week 96 for the Combined
Data from the View1 and View2 Studies



*) From Baseline to Week 52, Eylea was dosed every 8 weeks following 3 initial monthly doses. From Baseline to Week 52, ranibizumab 0.5 mg was dosed every 4 weeks. Beginning at Week 52, all groups were treated using a modified quarterly treatment paradigm where patients could be dosed as frequently as every 4 weeks but not less frequently than every 12 weeks based upon pre-specified retreatment criteria.

The proportion of patients at week 96 gaining at least 15 letters from baseline was 33.44% in the Eylea 2Q8 group, and 31.60% in the ranibizumab 0.5Q4 group.

In combined data analysis of the VIEW1 and VIEW2 studies Eylea demonstrated clinically meaningful changes from baseline in pre-specified secondary efficacy endpoint National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The magnitude of these changes was similar to that seen in published studies, which corresponded to a 15-letter gain in Best Corrected Visual Acuity (BCVA).

No clinically meaningful differences were found between Eylea and the reference product ranibizumab in changes of NEI VFQ-25 total score and subscales (near activities, distance activities, and vision-specific dependency) at week 52 from baseline.

Decreases in mean CNV area were evident in all dose groups in both studies.

Efficacy results in all evaluable subgroups (e.g. age, gender, race, baseline visual acuity, lesion type, lesion size) in each study and in the combined analysis were consistent with the results in the overall populations.

In the second year of the studies, efficacy was generally maintained through the last assessment at week 96.

In the second year of the studies, 2-4% of patients required all injections on a monthly basis, and a third of patients required at least one injection with a treatment interval of only one month.

Elderly Population

In the clinical studies, approximately 89% (1,616/1,817) of the patients randomised to treatment with Eylea were 65 years of age or older and approximately 63% (1,139/1,817) were 75 years of age or older.

Macular Oedema secondary to CRVO

The safety and efficacy of Eylea were assessed in two randomised, multi-centre, double-masked, sham-controlled studies in patients with macular oedema secondary to CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with Eylea) in the two studies COPERNICUS and GALILEO. In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg Eylea administered every 4 weeks (2Q4) or the control group receiving sham injections every 4 weeks for a total of 6 injections.

After 6 monthly injections, patients received treatment only if they met pre-specified retreatment criteria, except for patients in the control group in the GALILEO study who continued to receive sham (control to control) until week 52. Starting from this timepoint all patients were offered treatment if they met pre-specified criteria.

Patient ages ranged from 22 to 89 years with a mean of 64 years.

In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline.

Change in visual acuity at week 24 compared to baseline was a secondary efficacy variable in both COPERNICUS and GALILEO studies.

The difference between treatment groups was statistically significant in favour of Eylea in both studies. In both pivotal studies the maximal improvement in visual acuity has been achieved at month 3 with subsequent stabilisation of the effect on visual acuity and central retinal thickness until month 6. The statistically significant difference was maintained through week 52.

Detailed results from the analysis of both studies are shown in the Table and Figure below.

Table 4: Efficacy outcomes at week 24, week 52 and week 76/100 (Full Analysis Set with LOCF[C)]) in COPERNICUS and GALILEO studies

Efficacy Outcomes	**COPERNICUS**						**GALILEO**					
	24 Weeks		**52 Weeks**		**100 Weeks**		**24 Weeks**		**52 Weeks**		**76 Weeks**	
	Control (n = 73)	**Eylea 2 mg Q4 (n = 114)**	**Control[E)] (n = 73)**	**Eylea 2 mg (n = 114)**	**Control [E,F)] (n = 73)**	**Eylea [F)] 2 mg (n = 114)**	**Control (n = 68)**	**Eylea 2 mg Q4 (n = 103)**	**Control (n = 68)**	**Eylea 2 mg (n = 103)**	**Control [G)] (n = 68)**	**Eylea [G)] 2 mg (n = 103)**
Proportion of patients who gained at least 15 letters in BCVA[C)] from baseline	12%	56%	30%	55%	23.3%	49.1%	22%	60%	32%	60%	29.4%	57.3%
Weighted difference[A,B,E)] (95% CI)		44.8% (33.0, 56.6)		25.9% (11.8, 40.1)		26.7% (13.1, 40.3)		38.3% (24.4, 52.1)		27.9% (13.0, 42.7)		28.0% (13.3, 42.6)
p-value		p < 0.0001		p = 0.0006		p=0.0003		p < 0.0001		p = 0.0004		p=0.0004
Mean change in BCVA as measured by ETDRS[C)] letter score from baseline (SD)	-4.0 (18.0)	17.3 (12.8)	3.8 (17.1)	16.2 (17.4)	1.5 (17.7)	13.0 (17.7)	3.3 (14.1)	18.0 (12.2)	3.8 (18.1)	16.9 (14.8)	6.2 (17.7)	13.7 (17.8)
Difference in LS mean[A,C,D,E)] (95% CI)		21.7 (17.4, 26.0)		12.7 (7.7, 17.7)		11.8 (6.7, 17.0)		14.7 (10.8, 18.7)		13.2 (8.2, 18.2)		7.6 (2.1, 13.1)
p-value		p < 0.0001		p < 0.0001		p < 0.0001		p < 0.0001		p < 0.0001		p=0.0070

A) Difference is Eylea 2 mg Q4 weeks minus control

B) Difference and confidence interval (CI) are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)

C) BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LOCF: Last Observation Carried Forward
SD: Standard deviation
LS: Least square means derived from ANCOVA

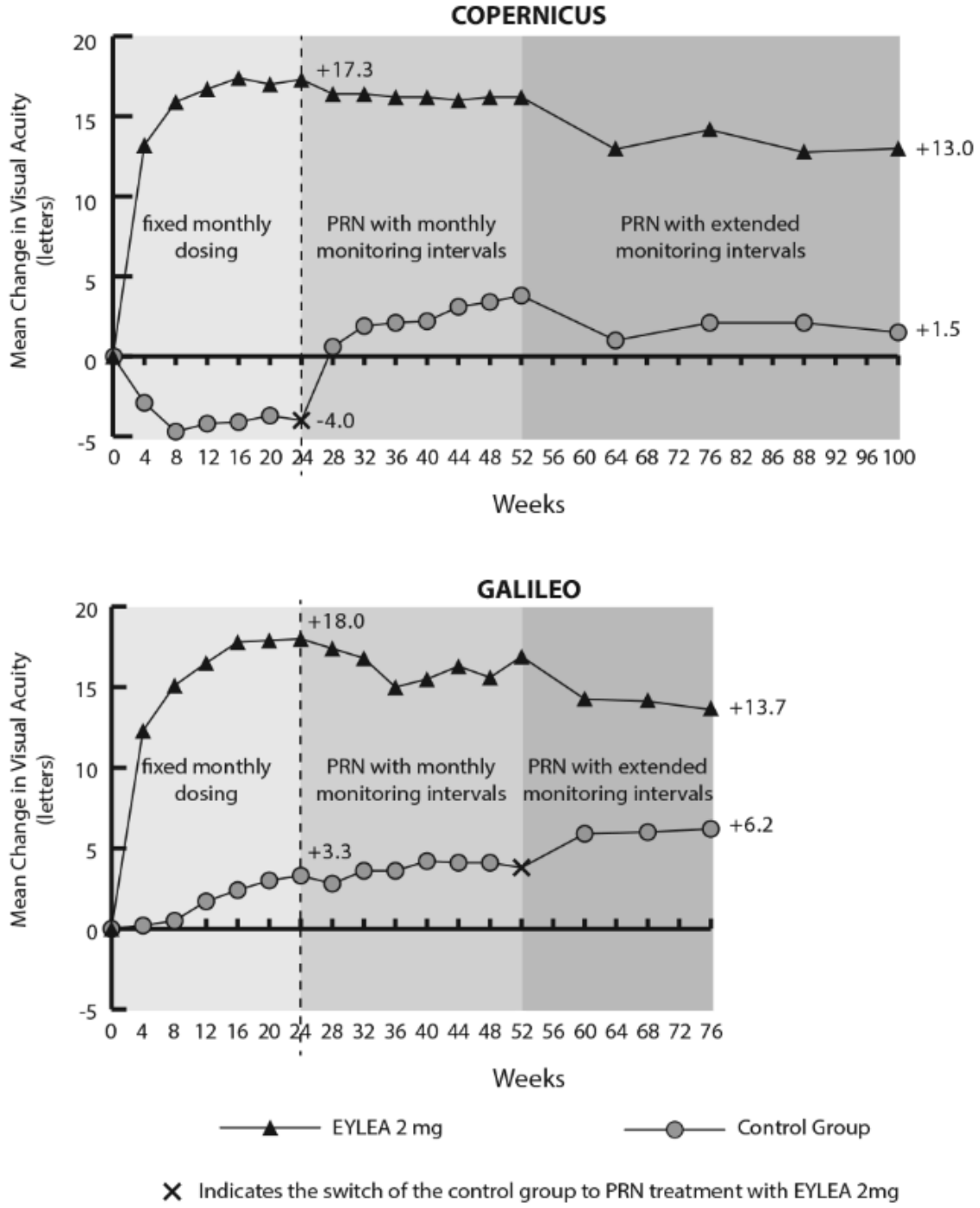
D) LS mean difference and confidence interval based on an ANCOVA model with factors treatment group, region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)

E) In COPERNICUS study, control group patients could receive Eylea on an as-needed basis as frequently as every 4 weeks during week 24 to week 52

F) In COPERNICUS study, both control group and Eylea 2mg patients received Eylea 2 mg on an as-needed basis as frequently as every 4 weeks starting from Week 52 to Week 88

G) In GALILEO study, both control group and Eylea 2mg patients received Eylea 2 mg on an as-needed basis every 8 weeks starting from Week 52 to Week 68.

Figure 2: Mean change from baseline to week 52 in visual acuity by treatment group for the COPERNICUS and GALILEO studies (Full Analysis Set)



The proportion of perfused patients in the Eylea group was high in the GALILEO study at baseline (86.4%; n = 89). Perfusion at week 24 primary endpoint was 91.8% (n = 89). The patients were largely able to maintain their perfusion status until week 76 (84.3%; n = 75). The number of perfused patients that started on sham was 79.4% (n = 54) at baseline. Perfusion at week 24 primary endpoint was 85.5% (n = 47). Patients in the sham group were switched to Eylea according to pre-specified criteria at week 52, 83,7% (n = 41) were perfused at this time. The patients were able to maintain their perfusion status until week 76 (84.0%; n = 42).

The proportion of perfused patients in the Eylea group in the COPERNICUS study at baseline was 67.5% (n = 77). Perfusion at week 24 primary endpoint was 87.4%; (n = 90). After week 24, patients in the Eylea group were treated according to pre-specified criteria. At week 100 76.8 % (n = 76) of patients were perfused. The percentage of perfused patients that started on sham was 68.5% (n = 50) at baseline. Perfusion at week 24 primary endpoint was 58.6% (n = 34). Patients in the sham arm were eligible to receive Eylea from week 24. The proportion of perfused patients increased to 83.9% (n = 47) at week 52 and was largely maintained until week 100 (78%; n = 39).

The beneficial effect of Eylea treatment on visual function was similar in the baseline subgroups of perfused and non-perfused patients.

In combined data analysis of the GALILEO and COPERNICUS studies, Eylea demonstrated clinically meaningful changes from baseline in pre-specified secondary efficacy endpoint National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The magnitude of these changes was similar to that seen in published studies, which corresponded to a 15-letter gain in Best Corrected Visual Acuity (BCVA).

Treatment effects in all evaluable subgroups (e.g. age, gender, race, baseline visual acuity, retinal perfusion status, CRVO duration) in each study were in general consistent with the results in the overall populations.

Elderly population

In the CRVO studies, approximately 52% (112/217) of the patients randomised to treatment with Eylea were 65 years of age or older, and approximately 18% (38/217) were 75 years of age or older.

Paediatric population

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

5.2 Pharmacokinetic properties

Eylea is administered directly into the vitreous to exert local effects in the eye.

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.

In a pharmacokinetic sub-study in 6 patients with frequent sampling, maximum plasma concentrations of free aflibercept (systemic C_{max}) were low, with a mean of approximately 0.02 microgram/ml (range 0 to 0.054) within 1 to 3 days after a 2 mg intravitreal injection, and were undetectable two weeks following dosage in almost all patients. Aflibercept does not accumulate in the plasma when administered intravitreally every 4 weeks.

The mean maximum plasma concentration of free aflibercept is approximately 50 to 500 times below the aflibercept concentration required to inhibit the biologic activity of systemic VEGF by 50% in animal models, in which blood pressure changes were observed after circulating levels of free aflibercept attained approximately 10 microgram/ml and returned to baseline when levels fell below approximately 1 microgram/ml. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100-fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF (2.91 microgram/ml) in a study of healthy volunteers. Therefore, systemic pharmacodynamic effects such as blood pressure changes are unlikely.

These pharmacokinetic results were confirmed in a pharmacokinetic sub-study in patients with CRVO (mean C_{max} of free aflibercept in plasma 0.046 microgram/ml (range: 0 to 0.081 microgram/mlL); undetectable concentrations reached within 1 week).

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

Free aflibercept binds VEGF to form a stable, inert complex. As with other large proteins, both free and bound aflibercept are expected to be cleared by proteolytic catabolism.

Renal impairment
No special studies in patients with renal impairment were conducted with Eylea.

Pharmacokinetic analysis of patients in the VIEW2 study, of which 40% had renal impairment (24% mild, 15% moderate, and 1% severe), revealed no differences with respect to plasma concentrations of active drug after intravitreal administration every 4 or 8 weeks.
Similar results were seen in patients with CRVO in the GALILEO study.

5.3 Preclinical safety data

Effects in non-clinical studies on repeated dose toxicity were observed only at systemic exposures considered substantially in excess of the maximum human exposure after intravitreal administration at the intended clinical dose indicating little relevance to clinical use.
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 based on C_{max} and AUC for free aflibercept were approximately 200- and 700-fold higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg. At the No Observed Adverse Effect Level (NOAEL) of 0.5 mg/eye in monkeys the systemic exposure was 42- and 56-fold higher based on C_{max} and AUC, respectively.

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

An effect of aflibercept on intrauterine development was shown in embryo-fetal 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 exposures based on C_{max} and cumulative AUC for free aflibercept were approximately 17- and 10-fold higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 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 4,900-fold and 1,500-fold higher, respectively, than the exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20
Sodium dihydrogen phosphate, monohydrate (for pH adjustment)
Disodium hydrogen phosphate, heptahydrate (for pH adjustment)
Sodium chloride
Sucrose
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

100 microlitres of solution in a vial (type I glass) with a stopper (elastomeric rubber), and an 18 G filter needle. Pack size of 1.

6.6 Special precautions for disposal and other handling

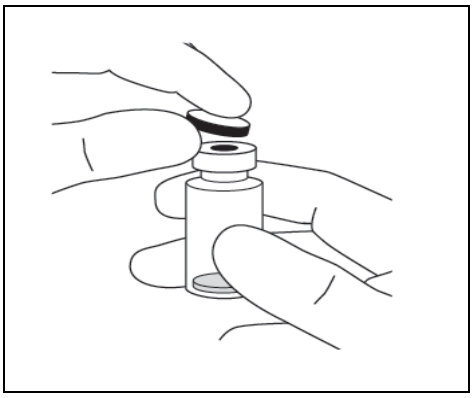
The vial is for single use only.
Since the vial contains more volume (100 microlitres) than the recommended dose (50 microlitres), a part of the volume contained in the vial has to be discarded prior to the administration.

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.

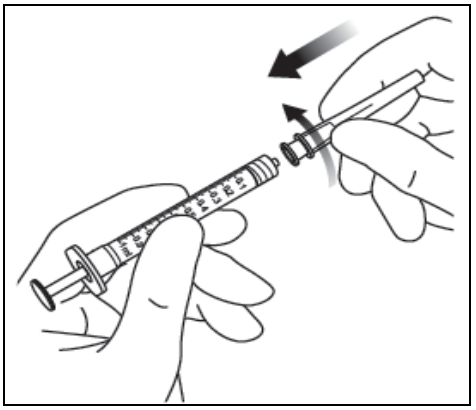
For the intravitreal injection, a 30 G x ½ inch injection needle should be used.

Instructions for use of vials:

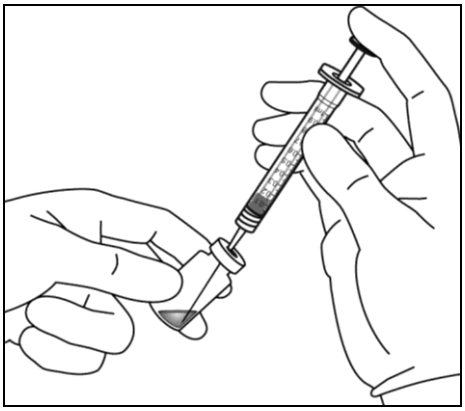
1. Remove the plastic cap and disinfect the outer part of the rubber stopper of the vial.

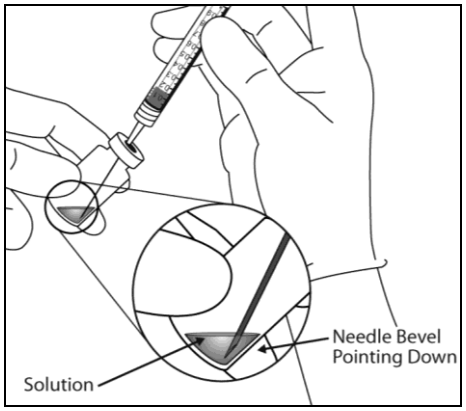


2. Attach the 18 G, 5-micron filter needle supplied in the carton to a 1-ml sterile, Luer-lock syringe.



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.

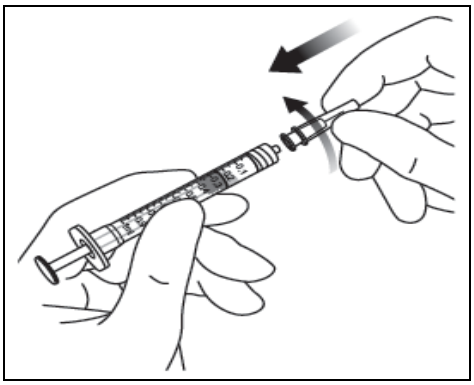




5. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

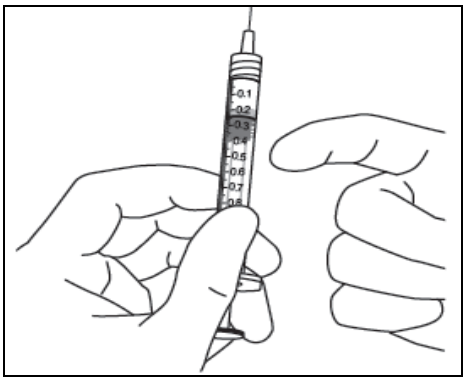
6. Remove the filter needle and properly dispose of it.
   Note: Filter needle is not to be used for intravitreal injection.

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

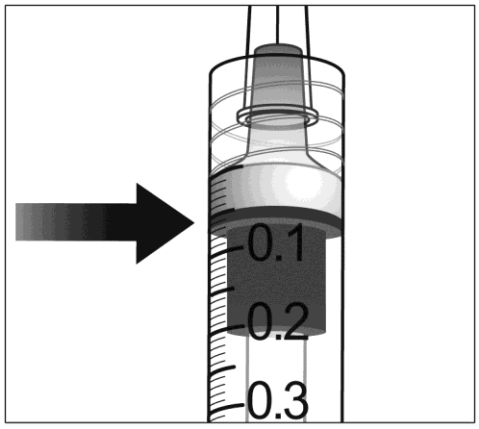


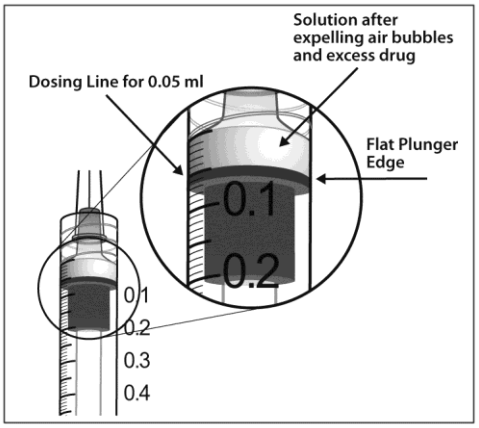
8. When ready to administer Eylea, remove the plastic needle shield.

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. Eliminate all bubbles and expel excess drug by slowly depressing the plunger so that the plunger tip aligns with the line that marks 0.05 ml on the syringe.





11. The vials are for single use only.
    Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Bayer Pharma AG, Mullerstrasse 178, 13353 Berlin, Germany

8. REGISTRATION HOLDER

Bayer Israel Ltd, 36 Hacharash St., Hod Hasharon 45240