ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

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

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

1 ml solution for injection contains 40 mg aflibercept*.

One pre-filled syringe contains 90 microlitres, equivalent to 3.6 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 injection (solution)

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).

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**

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.
Special population

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 indication wet AMD.

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 pre-filled syringe should only be used for the treatment of a single eye.

The pre-filled syringe contains more than the recommended dose of 2 mg. The extractable volume of the syringe (90 microlitres) is not to be used in total. The excess volume should be expelled before injecting. Injecting the entire volume of prefilled syringe 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 ≥ 30 mmHg). In all cases both 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 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.

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

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

Although the systemic exposure after ocular administration is very low, Eylea is not recommended 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 can not 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 a 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
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%).

Tabulated list of adverse reactions
The safety data described below include all adverse reactions from the wet AMD phase III studies with a reasonable possibility of causality to the injection procedure or medicinal product over a 96 weeks study duration.

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 patients).
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Hypersensitivity*)</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Conjunctival haemorrhage, Eye pain</td>
<td>Retinal detachment, Retinal pigment epithelium tear, Detachment of the retinal pigment epithelium, Retinal degeneration, Cataract, Cataract nuclear, Cataract subcapsular, 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</td>
<td>Endophthalmitis**), Retinal tear, Vitreous haemorrhage, Cataract cortical, Lenticular opacities, Corneal epithelium defect, Corneal erosion, Injection site irritation, Abnormal sensation in eye, Eyelid irritation, Vitritis, Uveitis, Iritis, Iridoocyclitis, Anterior chamber flare</td>
<td>Hypopyon</td>
</tr>
</tbody>
</table>

*) Including allergic reactions  
**) Culture positive and culture negative endophthalmitis

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

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 is characterized 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.
Clinical efficacy and safety
The safety and efficacy of Eylea were assessed in two randomized, 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 randomized 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: Efficacy outcomes at week 52 (primary analysis) and week 96; combined data from the VIEW1 and VIEW2 studies

<table>
<thead>
<tr>
<th>Efficacy Outcome</th>
<th><strong>Eylea 2Q8</strong>&lt;sup&gt;(c)&lt;/sup&gt;</th>
<th><strong>Ranibizumab 0.5Q4</strong>&lt;sup&gt;(c)&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Eylea 2 mg every 8 weeks following 3 initial monthly doses)</td>
<td>(ranibizumab 0.5 mg every 4 weeks)</td>
</tr>
<tr>
<td></td>
<td>(n = 607)</td>
<td>(n = 595)</td>
</tr>
<tr>
<td>Mean number of injections from baseline</td>
<td>7.6</td>
<td>12.3</td>
</tr>
<tr>
<td>Mean number of injections during second year (Week 52 to 96)</td>
<td>4.1</td>
<td>4.6</td>
</tr>
<tr>
<td>Proportion of patients with maintained visual acuity (&lt; 15 letters of BCVA&lt;sup&gt;A&lt;/sup&gt;) loss (Per Protocol Set)</td>
<td>95.33%&lt;sup&gt;(B)&lt;/sup&gt;</td>
<td>92.42%</td>
</tr>
<tr>
<td></td>
<td>Difference&lt;sup&gt;(c)&lt;/sup&gt;</td>
<td>0.9%</td>
</tr>
<tr>
<td></td>
<td>(95% CI)&lt;sup&gt;(D)&lt;/sup&gt;</td>
<td>(-1.7, 3.5)</td>
</tr>
<tr>
<td>Mean change in BCVA as measured by ETDRS&lt;sup&gt;A&lt;/sup&gt; letter score from baseline</td>
<td>8.40</td>
<td>8.74</td>
</tr>
<tr>
<td>Difference in LS&lt;sup&gt;(A)&lt;/sup&gt; mean change (ETDRS letters)&lt;sup&gt;(C)&lt;/sup&gt;</td>
<td>-0.32</td>
<td>-0.25</td>
</tr>
<tr>
<td></td>
<td>(95% CI)&lt;sup&gt;(D)&lt;/sup&gt;</td>
<td>(-1.87, 1.23)</td>
</tr>
<tr>
<td>Proportion of patients who gained at least 15 letters of vision from baseline</td>
<td>30.97%</td>
<td>33.44%</td>
</tr>
<tr>
<td></td>
<td>Difference&lt;sup&gt;(c)&lt;/sup&gt;</td>
<td>-1.5%</td>
</tr>
<tr>
<td></td>
<td>(95% CI)&lt;sup&gt;(D)&lt;/sup&gt;</td>
<td>(-6.8, 3.8)</td>
</tr>
</tbody>
</table>

<sup>A</sup> BCVA: Best Corrected Visual Acuity  
ETDRS: Early Treatment Diabetic Retinopathy Study  
LS: Least square means derived from ANCOVA  

<sup>B</sup> 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)  

<sup>C</sup> The difference is the value of the Eylea group minus the value of the ranibizumab group. A positive value favours Eylea.  

<sup>D</sup> Confidence interval (CI) calculated by normal approximation  

<sup>E</sup> After treatment initiation with three monthly doses  

<sup>F</sup> A confidence interval lying entirely above -10% indicates a non-inferiority of Eylea to ranibizumab  

<sup>G</sup> 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
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 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 randomized 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.
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 (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 $C_{\text{max}}$) 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.

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.

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 $C_{\text{max}}$ 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 $C_{\text{max}}$ and AUC, respectively.
No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept.

Aflibercept produced embryo-foetal toxicity (teratogenicity at all doses tested) in an embryo-foetal development study in pregnant rabbits with intravenous administration (3 to 60 mg/kg). At the lowest dose tested in this study (3 mg/kg) the systemic exposures based on C\text{max} and AUC for free aflibercept were approximately 2,900- and 600-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\text{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 pre-filled syringe in its blister and in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

90 microlitres of solution in pre-filled syringe (type I glass) marked with a black dosing line, with a plunger stopper (elastomeric rubber) and a Luer lock adaptor with a tip cap (elastomeric rubber). Pack size of 1.

6.6 Special precautions for disposal and other handling

The pre-filled syringe is for single use only.
Do not open sterile pre-filled blister outside the clean administration room.

Since the pre-filled syringe contains more volume (90 microlitres) than the recommended dose (50 microlitres), a part of the volume contained in the syringe 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 pre-filled syringe:**

1. When ready to administer Eylea, open the carton and remove the sterilized 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 sterilized 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: Snap off (do not turn or twist) 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. Remove the plastic needle shield.
7. 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.

8. To eliminate all bubbles and to expel 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).

9. The pre-filled syringe is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. **MARKETING AUTHORISATION HOLDER**

Bayer Pharma AG
D-13342 Berlin
Germany

8. **MARKETING AUTHORISATION NUMBER(S)**

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION**

10. **DATE OF REVISION OF THE TEXT**
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 injection (solution)

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).

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

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.

Special population

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 indication wet AMD.

**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. 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 ≥ 30 mmHg). In all cases both 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 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.

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

Pregnancy

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

Although the systemic exposure after ocular administration is very low, Eylea is not recommended 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 can not 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 a 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
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%).

Tabulated list of adverse reactions
The safety data described below include all adverse reactions from the wet AMD phase III studies with a reasonable possibility of causality to the injection procedure or medicinal product over a 96 weeks study duration.

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 patients)
### Description of selected adverse reactions

**Immune system disorders**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune system disorders</strong></td>
<td>Conjunctival haemorrhage, Eye pain</td>
<td>Retinal detachment, Retinal pigment epithelium tear, Detachment of the retinal pigment epithelium, Retinal degeneration, Cataract, Cataract nuclear, Cataract subcapsular, 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</td>
<td>Hypersensitivity*)</td>
<td>Endophthalmitis **), Retinal tear, Vitreous haemorrhage, Cataract cortical, Lenticular opacities, Corneal epithelium defect, Corneal erosion, Injection site irritation, Abnormal sensation in eye, Eyelid irritation, Vitritis, Uveitis, Iritis, Iridocyclitis, Anterior chamber flare</td>
</tr>
</tbody>
</table>

*) Including allergic reactions

**) Culture positive and culture negative endophthalmitis

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).

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

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

Pharmacodynamic effects

Wet AMD is characterized 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.

Clinical efficacy and safety
The safety and efficacy of Eylea were assessed in two randomized, 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 randomized 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>
<thead>
<tr>
<th>Efficacy Outcome</th>
<th>Eylea 2Q8</th>
<th></th>
<th>Ranibizumab 0.5Q4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Eylea 2 mg every 8 weeks following 3 initial monthly doses) (n = 607)</td>
<td>Ranibizumab 0.5 mg every 4 weeks) (n = 595)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 52 Mean number of injections from baseline</td>
<td>7.6</td>
<td>11.2</td>
<td>12.3</td>
<td>16.5</td>
</tr>
<tr>
<td>Week 96</td>
<td>11.2</td>
<td>4.1</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>Proportion of patients with maintained visual acuity (&lt; 15 letters of BCVA&lt;sup&gt;A&lt;/sup&gt;) loss (Per Protocol Set)</td>
<td>95.33%&lt;sup&gt;B&lt;/sup&gt;</td>
<td>92.42%</td>
<td>94.42%&lt;sup&gt;B&lt;/sup&gt;</td>
<td>91.60%</td>
</tr>
<tr>
<td>Difference&lt;sup&gt;C&lt;/sup&gt; (95% CI)&lt;sup&gt;D&lt;/sup&gt;</td>
<td>0.9% (-1.7, 3.5)&lt;sup&gt;F&lt;/sup&gt;</td>
<td>0.8% (-2.3, 3.8)&lt;sup&gt;F&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in BCVA as measured by ETDRS&lt;sup&gt;A&lt;/sup&gt; letter score from baseline</td>
<td>8.40</td>
<td>7.62</td>
<td>8.74</td>
<td>7.89</td>
</tr>
<tr>
<td>Difference in LS&lt;sup&gt;A&lt;/sup&gt; mean change (ETDRS letters)&lt;sup&gt;C&lt;/sup&gt; (95% CI)&lt;sup&gt;D&lt;/sup&gt;</td>
<td>-0.32 (-1.87, 1.23)</td>
<td>-0.25 (-1.98, 1.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients who gained at least 15 letters of vision from baseline</td>
<td>30.97%</td>
<td>33.44%</td>
<td>32.44%</td>
<td>31.60%</td>
</tr>
<tr>
<td>Difference&lt;sup&gt;C&lt;/sup&gt; (95% CI)&lt;sup&gt;D&lt;/sup&gt;</td>
<td>-1.5% (-6.8, 3.8)</td>
<td>1.8% (-3.5, 7.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>A</sup> BCVA: Best Corrected Visual Acuity  
ETDRS: Early Treatment Diabetic Retinopathy Study  
LS: Least square means derived from ANCOVA  
<sup>B</sup> 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)  
<sup>C</sup> The difference is the value of the Eylea group minus the value of the ranibizumab group. A positive value favours Eylea.  
<sup>D</sup> Confidence interval (CI) calculated by normal approximation  
<sup>E</sup> After treatment initiation with three monthly doses  
<sup>F</sup> A confidence interval lying entirely above -10% indicates a non-inferiority of Eylea to ranibizumab  
<sup>G</sup> 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 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 randomized 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.
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 (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 $C_{\text{max}}$) 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.

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.

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 $C_{\text{max}}$ 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 $C_{\text{max}}$ and AUC, respectively.
No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept.

Aflibercept produced embryo-foetal toxicity (teratogenicity at all doses tested) in an embryo-foetal development study in pregnant rabbits with intravenous administration (3 to 60 mg/kg). At the lowest dose tested in this study (3 mg/kg) the systemic exposures based on $C_{\text{max}}$ and AUC for free aflibercept were approximately 2,900- and 600-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 $C_{\text{max}}$ 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. **MARKETING AUTHORISATION HOLDER**

Bayer Pharma AG  
D-13342 Berlin  
Germany

8. **MARKETING AUTHORISATION NUMBER(S)***
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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 MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION
A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS 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 manufacturers responsible for batch release

Bayer Pharma AG
Müllerstraße 178
13353 Berlin
Germany

GP Grenzach Produktions GmbH
Emil-Barell-Straße 7
79639 Grenzach-Wyhlen
Germany

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

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.

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where EYLEA is marketed, at launch and after launch all ophthalmological clinics where EYLEA is expected to be used are provided with a physician information pack containing the following elements:

- Physician information
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information packs

The physician information should contain the following key elements:

- The Summary of Product Characteristics
- Sterile techniques, including periocular and ocular disinfection to minimise the risk of infection
- Use of antibiotics
- Use of povidone iodine or equivalent
- Techniques for the intravitreal injection
- Patient monitoring after intravitreal injection
- Key signs and symptoms of intravitreal injection related adverse events including endophthalmitis, increased intraocular pressure, conjunctival hemorrhage, eye pain, vitreous detachment, vitreous floaters, retinal pigment epithelium tear and traumatic cataract
- Management of intravitreal injection related adverse events

The patient information pack should be provided in both the form of a patient information booklet and an audio-CD that contain following key elements:

- Patient information leaflet
- How to prepare for EYLEA treatment
- What are the steps following treatment with EYLEA
- Key signs and symptoms of serious adverse events including endophthalmitis, increased intraocular pressure, conjunctival hemorrhage, eye pain, vitreous detachment, vitreous floaters, retinal pigment epithelium tear and traumatic cataract
- When to seek urgent attention from their health care provider

**OBLIGATION TO CONDUCT POST-AUTHORISATION MEASURES**

The MAH shall complete, within the stated timeframe, the following measures:

<table>
<thead>
<tr>
<th>Description</th>
<th>Due date</th>
</tr>
</thead>
<tbody>
<tr>
<td>To perform a post-authorisation randomised study with the primary objective of comparing the standard regime of injections every 8 weeks with a reactive regimen based on visual and anatomic outcomes, based on a CHMP approved protocol.</td>
<td>Final study report submission: 31 December 2017</td>
</tr>
</tbody>
</table>
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

Aflibercept

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

One pre-filled syringe contains 3.6 mg aflibercept in 90 microlitres (40 mg/ml) in iso-osmotic solution
Delivers a single dose of 2 mg/0.05 ml.
The excess volume should be expelled before injecting

1 pre-filled syringe (3.6 mg/90 microlitres)
Single dose: 2 mg/0.05 ml
Excess volume to be expelled.

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.

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 refrigerator (2°C to 8°C).
Do not freeze.
Keep the pre-filled syringe in its blister in the outer carton to protect from light.
Prior to use, the unopened blister may be stored at room temperature (below 25°C) for up to 24 hours.

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 Pharma AG
D-13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.
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

Aflibercept

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

One pre-filled syringe contains 3.6 mg/90 microlitres (40 mg/ml) in iso-osmotic solution.
Delivers a single dose of 2 mg/0.05 ml.
The excess volume should be expelled before injecting.

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.

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 refrigerator (2°C to 8°C).
Do not freeze.
Keep the pre-filled syringe in its blister in the outer carton to protect from light.
Prior to use, the unopened blister may be stored at room temperature (below 25°C) for up to 24 hours.

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 Pharma AG
D-13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS LABEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-filled Syringe</td>
</tr>
</tbody>
</table>

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Eylea 40 mg/ml solution for 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

Single dose = 2 mg/50 microlitres
3.6 mg/90 microlitres

6. OTHER
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

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

2. **STATEMENT OF ACTIVE SUBSTANCE**

Aflibercept

3. **LIST OF EXCIPIENTS**

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

4. **PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection in a vial (4 mg/100 microlitres)

One vial contains 4 mg aflibercept in 100 microlitres in iso-osmotic solution.
Delivers a single dose of 2 mg/0.05 ml.
The excess volume should be expelled before injecting

1 vial: 4 mg/0.1 ml
18G filter needle
Single dose: 2 mg/0.05 ml
Excess volume to be expelled.

5. **METHOD AND ROUTE OF ADMINISTRATION**

Intravitreal use.
Vial for single use only.
Read the package leaflet before use.

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 refrigerator (2°C to 8°C).
Do not freeze.
Keep the vial in the outer carton to protect from light.
Prior to use, the unopened vial may be stored at room temperature (below 25°C) for up to 24 hours.

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 Pharma AG
D-13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.
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 solution for 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

Single dose = 2 mg/50 microlitres
Extractable content = 4 mg/100 microlitres

6. OTHER
B. PACKAGE LEAFLET
Read all of this leaflet carefully before you start using 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.

What is in this leaflet
1. What Eylea is and what it is used for
2. What you need to know before you are given Eylea
3. How you will be given Eylea
4. Possible side effects
5. How to store Eylea
6. Contents of the pack and other information

1. What Eylea is and what it is used for

Eylea is a solution which is injected into the eye to treat an eye condition called neovascular (wet) age-related macular degeneration in adults, commonly referred to as wet AMD. 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 (PIGF), which, in excess, trigger 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.

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 stabilize, and in many cases, improve the vision loss related to wet AMD.

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:
- as injection with Eylea may trigger an increase in eye pressure (intraocular pressure) in some patients within 60 minutes of the injection. Your doctor should monitor this after each injection.
- if you have glaucoma.
- if you develop an infection inside the eye 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 risk factors for a special eye disease (retinal pigment epithelial tears), where Eylea will be given with caution.
- if you have a history of seeing flashes of light or floaters and if you have sudden increase of size and number of floaters.

When injecting VEGF inhibitors, substances similar to those contained in Eylea, into the body and not only into the eye, there is a potential 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. If any of the above applies to you, talk to your doctor before you are given Eylea.

**Children and adolescents**
The use of Eylea in children or adolescents under 18 has not been studied because wet AMD is a disease occurring only in elderly. Therefore there is no relevant use of Eylea in this age group for wet AMD.

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

**Pregnancy and breastfeeding**
- There is no experience of using Eylea in pregnant women. Eylea is not recommended 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.

- Eylea is not recommended during breastfeeding as it is not known whether Eylea passes into human milk. Ask your doctor for advice before starting Eylea treatment.

**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 (23 mg) of sodium per dose which means it is 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 (50 microlitres).

Eylea is administered as an injection into your eye (intravitreal injection) beginning with one injection per month for three consecutive doses, followed by one injection every two months.

After the first 12 months of treatment with Eylea, the treatment interval may be extended based on your doctor’s examination.

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.

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.
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.

The following is a list of the most serious side effects related to the injection procedure

**Uncommon (may affect up to 1 in 100 people):**
- infection or inflammation inside the eye (endophthalmitis)
- clouding of the lens due to injury (traumatic cataract)
- temporary increase of pressure inside the eye

In addition generalised allergic reactions (hypersensitivity) could potentially occur.

If you get any of these serious side effects, contact your doctor immediately.

The following is a list of the most common side effects

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

**Common (may affect up to 1 in 10 people):**
- detachment of the gel-like substance inside the eye from the retina (vitreous detachment)
- moving spots in vision (vitreous floaters)

The following is a list of the other side effects reported to be possibly related to the injection procedure or to the medicine.

**Common (may affect up to 1 in 10 people):**
- decreased sharpness of vision (detachment of the retina, retinal pigment epithelium tear, detachment of the retinal pigment epithelium)
- degeneration of the retina
- blurred vision (cataract nuclear)
- clouding of the lens (cataract subcapsular)
- damage of the front layer of the eyeball (corneal abrasion)
- swelling of the front layer of the eyeball (corneal oedema)
- injection site pain
- a feeling of having something in the eye
- increased tear production
- swelling of the eyelid
- bleeding at the injection site
- redness of the eye (ocular hyperaemia, conjunctival hyperaemia)
Uncommon (may affect up to 1 in 100 people):
- bleeding into the transparent gel that fills the space between the retina and the lens in the eye (vitreous haemorrhage)
- clouding of the lens (cataract cortical)
- disturbed/blurred vision (tear of the retina, lenticular opacities),
- injury of the front layer of the eyeball (corneal erosion, corneal epithelium defect)
- irritation at the injection site
- strange feeling in the eye
- irritation of the eyelid
- inflammation of certain parts of the eye (vitritis, uveitis, iritis, iridocyclitis, anterior chamber flare)

Rare (may affect up to 1 in 1,000 people):
- pus in the eye (hypopyon)

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 receiving blood thinners. This increased incidence was comparable between patients treated with ranibizumab and Eylea.

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

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.
- Prior to usage, the unopened blister may be stored at room temperature (below 25°C) for up to 24 hours.
- Keep the pre-filled syringe blister in its outer carton 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 90 microlitres, equivalent to 3.6 mg aflibercept. One pre-filled syringe delivers a dose of 2 mg aflibercept in 50 microlitres.
- The other ingredients are: polysorbate 20, sodium dihydrogen phosphate monohydrate (for pH adjustment), disodium hydrogen phosphate heptahydrate (for pH adjustment), sodium chloride, sucrose, water for injection.

What Eylea looks like and contents of the pack
Eylea is a solution for injection (solution) in pre-filled syringe (3.6 mg/90 microlitres). The solution is colourless to pale yellow.
Pack size of 1.
Marketing Authorisation Holder
Bayer Pharma AG
D-13342 Berlin
Germany

Manufacturer
GP Grenzach Produktions GmbH
Emil-Barell-Straße 7
D-79639 Grenzach-Wyhlen
Germany

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

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**France**
Bayer Santé
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**Malta**
Alfred Gera and Sons Ltd.
Tel: +356-21 44 62 05

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**Norge**
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Tlf: +47-24 11 18 00

**Österreich**
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Tel: +43-(0)1-711 460

**Polska**
Bayer Sp. z o.o.
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**Portugal**
Bayer Portugal S.A
Tel: +351-21-416 42 00

**România**
SC Bayer SRL
Tel: +40-(0)21-528 59 00

**Slovenija**
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Tel: +386-(0)1-58 14 400

**Slovenská republika**
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**Suomi/Finland**
Bayer Oy
Puh/Tél: +358-(0)20-78521

**Sverige**
Bayer AB
Tel: +46-(0)8-580 223 00
The following information is intended for healthcare professionals only:

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

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.

Prior to usage, the unopened blister of Eylea may be kept at room temperature (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 sterilized 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 sterilized 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: Snap off (do not turn or twist), 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. Remove the plastic needle shield.
7. 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.

8. To eliminate all bubbles and to expel 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).

9. The pre-filled syringe is for single use only.

   Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Read all of this leaflet carefully before you start using 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.

What is in this leaflet
1. What Eylea is and what it is used for
2. What you need to know before you are given Eylea
3. How you will be given Eylea
4. Possible side effects
5. How to store Eylea
6. Contents of the pack and other information

1. What Eylea is and what it is used for

Eylea is a solution which is injected into the eye to treat an eye condition called neovascular (wet) age-related macular degeneration in adults, commonly referred to as wet AMD. 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 (PIGF), which, in excess, trigger 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.

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 stabilize, and in many cases, improve the vision loss related to wet AMD.

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:

- as injection with Eylea may trigger an increase in eye pressure (intraocular pressure) in some patients within 60 minutes of the injection. Your doctor may monitor this after each injection.
- if you have glaucoma.
- if you develop an infection inside the eye 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 risk factors for a special eye disease (retinal pigment epithelial tears), where Eylea will be given with caution.
- if you have a history of seeing flashes of light or floaters and if you have sudden increase of size and number of floaters.

When injecting VEGF inhibitors, substances similar to those contained in Eylea, into the body and not only into the eye, there is a potential 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.

If any of the above applies to you, talk to your doctor before you are given Eylea.

**Children and adolescents**
The use of Eylea in children or adolescents under 18 has not been studied because wet AMD is a disease occurring only in elderly. Therefore there is no relevant use of Eylea in this age group for wet AMD.

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

**Pregnancy and breastfeeding**
- There is no experience of using Eylea in pregnant women. Eylea is not recommended 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.

- Eylea is not recommended during breastfeeding as it is not known whether Eylea passes into human milk. Ask your doctor for advice before starting Eylea treatment.

**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 (23 mg) of sodium per dose which means it is 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 (50 microlitres).
Eylea is administered as an injection into your eye (intravitreal injection) beginning with one injection per month for three consecutive doses, followed by one injection every two months.

After the first 12 months of treatment with Eylea, the treatment interval may be extended based on your doctor’s examination.

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.

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.
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.

The following is a list of the most serious side effects related to the injection procedure

**Uncommon (may affect up to 1 in 100 people):**
- infection or inflammation inside the eye (endophthalmitis)
- clouding of the lens due to injury (traumatic cataract)
- temporary increase of pressure inside the eye

In addition generalised allergic reactions (hypersensitivity) could potentially occur.

If you get any of these serious side effects, contact your doctor immediately.

The following is a list of the most common side effects

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

**Common (may affect up to 1 in 10 people):**
- detachment of the gel-like substance inside the eye from the retina (vitreous detachment)
- moving spots in vision (vitreous floaters)

The following is a list of the other side effects reported to be possibly related to the injection procedure or to the medicine.

**Common (may affect up to 1 in 10 people):**
- decreased sharpness of vision (detachment of the retina, retinal pigment epithelium tear, detachment of the retinal pigment epithelium)
- degeneration of the retina
- blurred vision (cataract nuclear)
- clouding of the lens (cataract subcapsular)
- damage of the front layer of the eyeball (corneal abrasion)
- swelling of the front layer of the eyeball (corneal oedema)
- injection site pain
- a feeling of having something in the eye
- increased tear production
- swelling of the eyelid
- bleeding at the injection site
- redness of the eye (ocular hyperaemia, conjunctival hyperaemia)
Uncommon (may affect up to 1 in 100 people):
- bleeding into the transparent gel that fills the space between the retina and the lens in the eye (vitreous haemorrhage)
- clouding of the lens (cataract cortical)
- disturbed/blurred vision (tear of the retina, lenticular opacities)
- injury of the front layer of the eyeball (corneal erosion, corneal epithelium defect)
- irritation at the injection site
- strange feeling in the eye
- irritation of the eyelid
- inflammation of certain parts of the eye (vitritis, uveitis, iritis, iridocyclitis, anterior chamber flare)

Rare (may affect up to 1 in 1,000 people):
- pus in the eye (hypopyon)

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 receiving blood thinners. This increased incidence was comparable between patients treated with ranibizumab and Eylea.

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

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.
- Prior to usage, the unopened vial may be stored at room temperature (below 25°C) for up to 24 hours.
- Keep the vial in its outer carton 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 100 microlitres, equivalent to 4 mg aflibercept. One vial delivers a dose of 2 mg aflibercept in 50 microlitres.
- The other ingredients are: polysorbate 20, sodium dihydrogen phosphate monohydrate (for pH adjustment), disodium hydrogen phosphate heptahydrate (for pH adjustment), sodium chloride, sucrose, water for injection.

What Eylea looks like and contents of the pack
Eylea is a solution for injection (solution) in a vial (4 mg/100 microlitres). The solution is colourless to pale yellow.
Pack size of 1.
Marketing Authorisation Holder
Bayer Pharma AG
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Manufacturer
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The following information is intended for healthcare professionals only:

Each vial should only be used for the treatment of a single eye. The solution should be inspected visually for any foreign particulate matter and/or discoloration or any variation in physical appearance prior to administration. In the event of either being observed, discard the medicinal product.

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. 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 onto 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 medicinal product 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.