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Aflibercept Durability in Macular Diseases

A focus on real-life evidence

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Introduction

The development of anti-vascular endothelial growth factor (VEGF) agents as treatment for various diseases involving the macula has been a tremendous advance considering the huge and growing burden associated with these conditions. Results from clinical trials using aflibercept solution for injection EYLEA® (aflibercept solution for injection) to treat neovascular age-related macular degeneration (AMD), visual impairment due to diabetic macular oedema (DME), and visual impairment due to macular oedema secondary to retinal vein occlusion (RVO), branch and central RVO suggest it offers potential benefits over other anti-VEGF options.

To highlight real-life evidence from the use of aflibercept to treat these diseases, Bayer HealthCare supported a scientific symposium during the 6th World Congress on Controversies in Ophthalmology (COPHy) held in Sorrento, Italy, 26–29 March 2015. Presentations were given by an international faculty of respected opinion leaders in the field who reviewed their evidence-based experiences and shared case studies of patients treated with aflibercept and comparing it with other anti-VEGF drugs.

Aflibercept: A VEGF Receptor Decoy

Aflibercept is a synthetic fully humanised fusion protein of 2 VEGF receptor domains [VEGF receptor 1 (VEGF-R1) and (VEGF-R2)] with the Fc portion of human immunoglobulin G1 (IgG1). It has been specifically designed to block 2 members of the VEGF family: placental growth factor (PlGF) and, primarily, VEGF-A.1,2 (See Figure 1) VEGF-A, which binds to both VEGF-R1 and VEGF-R2, has effects on angiogenesis and vascular permeability that have both pathophysiologic implications in disease and importance in normal physiology.2 PlGF also has proangiogenic activity, which is completely mediated through VEGF-R1.2 Currently, it is unknown whether the proangiogenic capability of PlGF has any clinical relevance.

Characteristics of anti-VEGF biologic drugs

Two anti-VEGF agents are currently approved for intravitreal injection: aflibercept and ranibizumab (Lucentis®, Novartis). Bevacizumab (Avastin®, Roche) is also used intravitreally, however is unlicensed for use in the eye. Differences in the binding profiles and molecular characteristics of these agents have potential clinical implications. Unlike aflibercept, bevacizumab and ranibizumab bind only VEGF-A, and of the 3 agents, aflibercept has the highest VEGF-A binding affinity, even exceeding that of the native receptors.2 Furthermore, aflibercept has strict 1:1 stoichiometric binding,2 that is, aflibercept binds to a VEGF-A dimer on both sides “like a trap,” explained Professor...
Sascha Fauser (University Hospital of Cologne, Germany). By comparison, bevacizumab can “daisy chain” or “paper doll” with VEGF leading to large, multimeric conglomerates, and 2 ranibizumab molecules can bind each VEGF dimer, he said. (See Figure 2).

Structurally, both aflibercept and bevacizumab contain the Fc domain of IgG1, whereas ranibizumab is an antibody fragment without the Fc domain. “Although the Fc domain could trigger complement activation, whether this is relevant in humans is, as yet, unknown,” Prof. Fauser said.

The 3 anti-VEGF agents also differ in size, with bevacizumab having the highest molecular weight and ranibizumab the lowest. “With regard to retinal penetration, a small molecule is theoretically preferable, but perhaps it is sufficient for the drug to inhibit VEGF in the vitreous,” said Prof. Fauser.

**Duration of intravitreal VEGF suppression**

Regarding duration of intravitreal VEGF suppression, theoretically the longer the better, as longer activity could support a longer dosing interval that would reduce treatment burden for patients. The intravitreal half-lives of ranibizumab, bevacizumab, and aflibercept have been estimated to be 3.2, 5.6, and 4.8 days, respectively. Duration of VEGF suppression, however, also depends on VEGF binding affinity, and data from mathematical modeling and clinical studies indicate that compared to ranibizumab and bevacizumab, aflibercept has much longer biologic activity in the eye.

Prof. Fauser said that all of the anti-VEGF agents will, in the beginning, block all VEGF that is present in the eye because the amount of drug injected into the vitreous is “huge” compared with the amount of VEGF. For example, a 2-mg dose of aflibercept results in an intravitreal concentration of about 400 million pg/mL, whereas the concentration of VEGF is about 50 pg/mL. “After many half-lives, binding affinity matters [with respect to duration of functional activity],” he said.

Modeling incorporating intravitreal half-lives and relative equimolar VEGF-binding activities predicts that ranibizumab and bevacizumab might work for about 27 to 38 days, whereas aflibercept would inhibit VEGF for 10 to 12 weeks. These calculations are consistent with results of clinical studies conducted by Prof. Fauser and colleagues in which they assayed aqueous humor VEGF levels as a measure of intravitreal VEGF suppression in patients being treated with intravitreal anti-VEGF injections. Their methodology was based on previous work showing cytokine levels in the aqueous correlate with vitreous levels.

In a study including 47 patients treated with ranibizumab, there was significant interpatient variation in the duration of VEGF suppression, with a range from 26 to 49 days. The mean VEGF suppression time was 38 days, and measurements obtained over treatment periods of up to 3 years showed long-term stability of VEGF suppression time within individual patients. The long-term data also showed there were no rebound effects or tachyphylaxis.

Prof. Fauser performed the same study in a group of 17 patients being treated with ranibizumab for DME, and the results showed a similar range of VEGF suppression times, but with a shift in the distribution towards shorter suppression times so that the mean was only 34 days. The higher VEGF levels in DME relative to exudative AMD result in a higher demand for anti-VEGF treatment, he said.

Next, the same methods were used to study 27 patients with AMD being treated with aflibercept for neovascular AMD. The results showed a minimum VEGF suppression time of >40 days and an average VEGF suppression time of 71 days. Work is currently being undertaken to try to elucidate the correlation between duration of VEGF inhibition and clinical parameters. Prof. Fauser explained that differences between drugs are difficult to identify from available clinical studies because they mostly used a fixed monthly injection interval.

**Systemic VEGF exposure**

Anti-VEGF drugs injected into the vitreous enter into the systemic circulation where the concentration of free VEGF in the plasma is also approximately 50 pg/mL. Available data for all 3 anti-
VEGF drugs indicate that VEGF levels in plasma drop fairly soon after intravitreal injection. Although the suppression of plasma free VEGF is reported as being greater for aflibercept than for bevacizumab and ranibizumab, no alarming systemic safety signals have been seen in the numerous studies addressing this concern. Prof. Fauser offered, therefore, that having lower circulating VEGF levels for a certain period of time may not be as problematic as previously thought.

**Summary**

Summarising these data, Prof. Fauser stated that the clinical relevance of PlGF binding by aflibercept is unclear, as is the systemic suppression of VEGF with any of the anti-VEGF agents. The prolonged biologic activity of aflibercept for suppressing VEGF in the eye when compared with other anti-VEGF agents (eg, >71 days for aflibercept vs 37 days for ranibizumab) is explained by aflibercept’s high VEGF-binding affinity. Finally, intraocular VEGF suppression times in individual patients are stable over treatment periods of at least 1 to 3 years with no signs of tachyphylaxis or rebound effects.

**Aflibercept in the Real-World Setting: Wet AMD Outcomes from UK Hospitals**

Outcomes of patients treated for wet AMD (wAMD) with aflibercept at 13 centres participating in the UK National Aflibercept Audit were presented by Mr. Faruque Ghanchi (Bradford Teaching Hospitals, Bradford, UK). Mr. Ghanchi acknowledged support from Miss Devonport, Miss Setty, and Mr. Mookhtiyar, consultants at the Macula Service, Bradford Teaching Hospitals.

The UK National Aflibercept Audit comprises centres that are prospectively collecting data to determine visual and anatomic outcomes achieved in clinical practice using the approved licensed dose of aflibercept to treat wAMD. The licensed posology for aflibercept for wAMD reflects the regimen used in the pivotal VIEW study protocol. It is 2 mg, initiated with 1 injection per month for 3 consecutive doses, followed by 1 injection every 2 months for the first year. There is no requirement for monitoring between injections. After the first 12 months of treatment, the treatment interval may be extended based on visual and/or 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.

Mr. Ghanchi stated that data from clinical trials suggest that administering ranibizumab without strict monthly follow-up leads to suboptimal outcomes when treating wAMD. In clinical practice, however, it is not always possible to achieve the monthly schedule.” Mr. Ghanchi said.

**Bradford centre experience**

Mr. Ghanchi presented data from his centre in Bradford for 323 patients treated with aflibercept by 4 retina specialists. Mean baseline VA was 51.1 letters. Among 40 eyes that had reached the 1-year visit, mean VA was 60.3 letters. The improvement is consistent with the VA change observed in the VIEW study where patients treated with aflibercept with the licensed posology gained an average of about 8.4 letters from baseline after the first year. Some patients were switched to aflibercept from ranibizumab because they were deemed to have a poor response (downward trend in VA) despite receiving frequent injections of ranibizumab. At 8 months after the switch to aflibercept, mean VA improved by about 5 letters.

Another analysis focused on patients who initially were treated in one eye only, but subsequently developed wAMD in the fellow eye and began receiving aflibercept bilaterally. After 1 year, mean VA improvement from baseline was better in the first eyes than in the second eyes (9.4 vs 6.3 letters, respectively). The difference is explained by the fact that treatment was initiated earlier in the second eyes, before more severe vision loss. Mean VA when starting aflibercept was 50.0 letters in the first eyes and 61.1 letters in the second eyes.

Patients achieving 70+ letters are of particular interest as that level of vision (equivalent to VA >6/12) correlates to the cutoff for maintaining a driving licence in the UK. Mr. Ghanchi said. At 1 year after starting aflibercept treatment, VA was 70+ letters in about 27% of patients, which is slightly less than the proportion seen in the VIEW study.

At 1 year, the proportion of patients with a VA gain ≥15 letters from baseline was higher in the Bradford cohort than in the VIEW study, 38% vs 31%, respectively. The proportion of patients with a VA loss ≥3 lines after 1 year was 7% at the Bradford centre, which is comparable to the VIEW data.

In the VIEW study, patients treated with aflibercept 2 mg, beginning with 3 consecutive monthly injections followed then with injections every 2 months, received an average of 7.5 injections and had an average of 8 visits during the first year. In the Bradford cohort, the median number of patient visits during the first year was 5.4 and the median number of injections was also 5.4.

**UK multicentre data**

Mr. Ghanchi also presented pooled data from 3514 eyes treated at 6 UK centres participating in the National Aflibercept Audit, of which 571 eyes have follow-up to 1 year. Mean baseline VA was 54 letters, slightly better than in the cohort treated at the Bradford centre, and the mean VA gain from baseline at 1 year was 5.7 letters.

When patients were stratified into 4 groups according to their baseline VA (<35, 35–55, 56–70, and >70 letters), those who presented with the poorest VA had the greatest gain (~14 letters) whereas, the gain in VA was modest (1.5 letters) in eyes with the best VA at baseline. The multicentre data also showed that among patients who went on to receive treatment in both eyes, the mean VA gain after 1 year was somewhat better in the first eye than in the second eye (6.4 vs 2.9 letters, respectively). Almost 35% of patients followed to 1 year achieved VA of 70+ letters, similar to what was found in the VIEW study. The results...
were also similar in the multicentre cohort compared to VIEW for proportion of patients achieving ≥3 lines of VA improvement. At 1 year in the multicentre audit, about 20% of eyes gained ≥3 lines from baseline and about 7% lost ≥3 lines from baseline. Thus, VA was stable or improved in more than 90% of eyes after 1 year of treatment with aflibercept.

The majority of centres in the UK have been following the VIEW injection protocol, that is, the administration of 3 loading doses followed by fixed dosing at 2-month intervals. The median number of patient visits in the first year was 8. The mean number of injections was 6.2 and the median was 7.

In the pooled cohort, there were about 3100 eyes switched to aflibercept because of a poor response to another anti-VEGF agent. Almost half of those eyes had been on their prior anti-VEGF therapy for more than 1 year, and their mean visual acuity overall showed a downward trend. At 1 year after switching to aflibercept, mean VA was improved by about 1.5 letters.

First-year summary
Mr. Ghanchi concluded that the real-world experience from the prospective audit shows that aflibercept has been very effective in treating wAMD in a large cohort of patients. VA outcomes have been on par with the VIEW study, but with less treatment burden and fewer visits to the clinic than with ranibizumab treatment requiring monthly monitoring.

Importantly, according to Mr. Ghanchi, “Aflibercept has been found to be particularly useful for patients who were poorly responsive to previous anti-VEGF treatment. For a large cohort, vision is maintained, whereas for some, vision is improved.”

The Swiss Perspective: Real-Life Experiences in CRVO

The presentation by Professor Stephan Michels (University of Zurich, Switzerland) covered the clinical approach used at the City Hospital Triemli, Zurich, for treating visual impairment due to macular oedema secondary to CRVO.

In the EU, the aflibercept posology for visual impairment due to macular oedema secondary to CRVO recommends 2 mg given monthly, continuing until maximum VA is achieved and/or there are no signs of disease activity. Three or more consecutive, monthly injections may be needed. Treatment may then be continued with a treat and extend (TAE) regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes. If visual and anatomic outcomes indicate that the patient is not benefiting from initial monthly injections, aflibercept should be discontinued.

Aflibercept in CRVO: GALILEO and COPERNICUS key conclusions

GALILEO and COPERNICUS, the pivotal studies leading to the approval of aflibercept for treatment of visual impairment due to macular oedema secondary to CRVO, showed aflibercept-treated patients had rapid improvements in vision and oedema after the first injection that were sustained at 1 year. Prof. Michels noted, however, that the injection protocol used in the pivotal studies, which involved 6 consecutive monthly injections followed by variable treatment as needed, does not necessarily correspond to regimens used in clinical practice. In addition, he pointed out that he has learned through clinical experience the importance of treating patients early to maximize their outcome by limiting permanent structural damage and vision loss.

CRVO case study

Prof. Michels presented a case study of a patient with a non-ischaemic CRVO whom he had been treating for several years. The patient presented in October 2010 with poor VA (20/63) and extensive oedema. At that time, there were no approved treatments for macular oedema secondary to CRVO, but the patient was started on off-label treatment with monthly injections of bevacizumab. After 8 injections, his VA improved to 20/40, but he had persistent macular oedema, which led Prof. Michels to wonder if the patient was an insufficient responder to anti-VEGF therapy.

Nevertheless, when ranibizumab was approved for the treatment of visual impairment due to macular oedema secondary to CRVO, the patient was switched to that anti-VEGF agent. After 12 ranibizumab injections, given on a monthly basis, the oedema was completely resolved and VA improved to 20/32. Prof. Michels tried to extend the treatment interval to 6 weeks, but when the patient returned for follow-up, the oedema had recurred. He was put back on monthly ranibizumab and achieved 20/20 VA after receiving a total of 19 ranibizumab injections. The patient was pleased with the outcome but not with the monthly visits to the clinic.

Therefore, Prof. Michels switched the patient to aflibercept, employing a TAE approach. After the first injection, the patient was seen after 6 weeks with a plan to extend the time to follow-up by 2 weeks after each visit if his retina remained dry. At 10 weeks after receiving his third aflibercept injection, the patient’s VA was 20/20, and the follow-up interval was then extended to 12 weeks. However, the oedema had returned at the next visit.

“This patient’s course indicates that macular oedema secondary to CRVO is a chronically recurrent problem,” said Prof. Michels.

The patient was switched back to a 10-week follow-up interval, at which he was kept for some time. In April 2014, the patient returned to the clinic 11 weeks after his last aflibercept injection and his macula was still dry. Thereafter, Prof. Michels was able to extend the patient to retreatment at 13-week intervals, and in December 2014, the patient had 20/20 VA and the macula was totally dry.

In summary, within the first 26 months, the patient required 27 injections of bevacizumab or ranibizumab and had a maximum recurrence-free interval of just 4 weeks. Within the last 24 months while being treated with aflibercept, the patient required only 10 injections and had a maximum recurrence-free interval of 13 weeks. When follow-up was extended to 14 weeks, he developed recurrent oedema.
"So the niche is very small, and despite almost 4 years of anti-VEGF treatment, the patient still had recurrent oedema," concluded Prof. Michels.

Subpopulation — nonresponsive to other anti-VEGF therapy
Prof. Michels also presented outcomes for a group of 13 patients who were “nonresponsive or poorly responsive” to ranibizumab or bevacizumab. These patients required frequent retreatment, at least every 6 weeks, and although they had improvements in VA and oedema, they still had some persistent oedema.

All 13 patients were switched to aflibercept, and after the first aflibercept injection, mean VA improved about 10 letters. During follow-up to 12 months after switching to aflibercept and with initiation of a treat and extend regimen there was further dramatic reduction in central retinal thickness.

“Aflibercept treatment of visual impairment due to macular oedema secondary to CRVO leads to rapid and sustained improvement in VA and retinal thickness. In addition, it seems to have an add-on effect, particularly with regard to extending recurrence-free intervals, in eyes pretreated with other anti-VEGF agents that may have been considered nonresponders,” concluded Prof. Michels.

Conclusion—TAE with aflibercept in CRVO
Data and experience suggest aflibercept has several advantages over other anti-VEGF agents in treating visual impairment due to macular oedema secondary to CRVO. Its key benefit is longer durability, said Prof. Michels.

He also stated that TAE appears to be the ideal treatment concept in this indication, although there is no certainty as to how far it can be extended.

“Individualisation is key when treating macular oedema secondary to CRVO. TAE permits clinicians to find the individual recurrence-free interval while maintaining a dry retina, preventing vision loss due to recurrence, minimizing the number of injections, and reducing the number of follow-up visits,” Prof. Michels said. [see SIDEBAR for pearls on treating CRVO]

Treating DME — Real-Life Cases
“Kentucky is really affected by the diabetes epidemic, and so we have a unique perspective on treating diabetic-related eye disease,” said Dr. John Kitchens (Retina Associates of Kentucky, Lexington, US).

The experience and insight gained from these cases provided the content for Dr. Kitchens’ presentation describing his own clinical approach to treating visual impairment due to DME.

Aflibercept was approved for treating visual impairment due to DME based on the VIVID-DME and VISTA-DME trials in which aflibercept 2 mg monthly and aflibercept 2 mg every 2 months after 5 loading doses were compared against macular laser photocoagulation as the control group.25 The outcomes with aflibercept were excellent at 1 year: patients gained an average of >2 lines of VA from baseline, and 30% to 40% of patients gained 3+ lines of VA, which is comparable to results associated with other anti-VEGF agents.

The posology of aflibercept for the treatment of visual impairment due to DME is the same in the US as in the EU: 5 monthly injections (2 mg) followed by 1 injection every 2 months. There is no requirement for monitoring between injections. According to the EU posology, after the first 12 months of treatment with aflibercept, the treatment interval may be extended based on visual and/or anatomic outcomes.

For ranibizumab, however, there are some differences between dosing in the EU and in the US. The recommended dose of ranibizumab for treatment of visual impairment due to DME is 0.3 mg in the US, whereas it is 0.5 mg in the EU.

A step back in time
The Diabetic Retinopathy Clinical Research (DRCR) network includes in excess of 100 practices in the US and Canada, and comprises more than 300 physicians who are trying to better understand how to treat patients with diabetic retinopathy (DR) and DME.

The DRCR Protocol I study looked at whether anti-VEGF therapy with ranibizumab 0.5 mg plus prompt laser or deferred laser (deferred >6 months) was equal to or better than intravitreal steroids with prompt laser or prompt laser alone.24 Data from follow-up to 2 years showed that intravitreal ranibizumab was far superior to intravitreal triamcinolone combined with laser or laser alone for improving VA.25 The outstanding responses to anti-VEGF therapy were maintained with follow-up to 5 years, but particularly remarkable was the decreasing frequency of ranibizumab injections over time.26 Although patients in the deferred laser group required a median of 9 injections in the first year, they received a median of only 6 injections during the ensuing 4 years, with a median of 0 injections in the fifth year.27 These data suggest that anti-VEGF treatment may permanently modify the disease in a positive way, Dr. Kitchens said.

Case studies—Aflibercept treatment of visual impairment due to DME
Dr. Kitchens described 3 cases in which patients benefited after changing from their existing anti-VEGF therapy to aflibercept.

One 68-year-old woman was switched to aflibercept for bilateral treatment of visual impairment due to DME after extensive prior treatment, including 23 injections of ranibizumab in each eye and grid laser in her right eye. She originally started on monthly ranibizumab injections, and in the middle of her course of treatment, the ranibizumab injection interval was extended to about every 6 weeks.* Once aflibercept was approved for treatment of DME, her treatment was switched because she showed signs of worsening while on ranibizumab. After receiving her first aflibercept injections bilaterally, the patient missed her next scheduled appointment and did not return for 12 weeks, at which time she reported she was seeing so well that she did not feel the need to return earlier. When seen at 12 weeks after her first intravitreal aflibercept injections, she had visual and anatomic improvements in

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both eyes. (See Figure 5)

Another patient who had DME with nonproliferative DR in his right eye had received intravitreal triamcinolone, panretinal photocoagulation, and 18 ranibizumab injections along with multiple bevacizumab injections between January 2010 and August 2014. While receiving ranibizumab every 4 weeks, he did fairly well, but he still had residual focal oedema around the fovea and just nasal to the fovea. When the ranibizumab injection interval was extended to 6 weeks, his VA improved but his oedema recurred.

The patient was switched to intravitreal aflibercept in August 2014, and was not able to return for 8 weeks, at which time his oedema was much improved and his VA was stable.

The final case presented by Dr. Kitchens involved a woman with severe bilateral DME with VAs of 20/200 and 20/50. She was first treated in June 2012 and started with bevacizumab injections every 4 weeks. After failing to achieve a sufficient response, she was switched to ranibizumab injections every 4 weeks, which resulted in significant reduction of oedema.

She was switched to aflibercept when it was approved by the FDA for treatment of visual impairment due to DME, and with dosing every 4 weeks had further reduction in oedema. After the aflibercept dosing interval was extended, the oedema was further reduced, and the patient’s VA stabilised at 20/40. She is being maintained on aflibercept every 8 to 9 weeks and is happy with the reduced treatment and visit burden.

**Conclusion—Aflibercept treatment of visual impairment due to DME**

The retina specialists in our practice began using aflibercept to treat DME after it received FDA approval for that indication in July, 2014. As highlighted by these selected cases from our initial experience, aflibercept has been a valuable addition, and it is now the most commonly used anti-VEGF agent in our clinic for patients with visual impairment due to DME.

**References**


20. U. Schmidt-Erfurth et al., Efficacy and safety of monthly versus


Withhold treatment in patients with: rhemagmatogenous retinal detachment or stage 3 or 4 macular holes; with retinal break and do not resume treatment until the break is adequately repaired. Withhold treatment and do not resume before next scheduled treatment if there is: decrease in best-corrected visual acuity ≤30 letters compared with the last assessment; central foveal subretinal haemorrhage, or haemorrhage ≥50%, of total lesion area. Do not treat in the 28 days prior to or following performed or planned intraocular surgery. Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection. Populations with limited data: There is limited experience of treatment with Eylea in patients with ischaemic, chronic RVO. In patients presenting with clinical signs of irreversible ischaemic visual function loss, aflibercept treatment is not recommended. There is limited experience in DMO due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy. Eylea has not been studied in patients with active systemic infections, concurrent eye conditions such as retinal detachment or macular hole, in diabetic patients with uncontrolled hypertension. This lack of information should be considered when treating such patients. Interactions: No available data. Fertility, pregnancy & lactation: Not recommended during pregnancy unless potential benefit outweighs potential risk to the foetus. No data available in pregnant women. Studies in animals have shown embryo-fetal toxicity. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last injection. Not recommended during breastfeeding. Excretion in human milk: unknown. Male and female fertility impairment seen in animal studies with high systemic exposure not expected after ocular administration with very low systemic exposure. Effects on ability to drive and use machines: Possible temporary visual disturbances. Patients should not drive or use machines if vision inadequate. Undesirable effects: Very common: conjunctival haemorrhage (phase III studies: increased incidence in patients receiving anti-thrombotic agents), visual acuity reduced. Common: retinal pigment epithelial tear, detachment of the retinal pigment epithelium, retinal degeneration, vitreous haemorrhage, cataract (nuclear or subcapsular), corneal abrasion or erosion, corneal oedema, increased intraocular pressure, blurred vision, vitreous floaters, vitreous detachment, injection site pain, eye pain, foreign body sensation in eyes, increased lacrimation, eyelid oedema, injection site haemorrhage, punctate keratitis, conjunctival or ocular hyperaemia. Uncommon: Injection site irritation, abnormal sensation in eye, eyelid irritation. Serious: cf. CI/JP & - additional: blindness, endophthalmitis, cataract traumatic, transient increased intraocular pressure, vitreous detachment, retinal detachment or tear, hypersensitivity (incl. allergic reactions), vitreous haemorrhage, cortical cataract, lenticular opacities, corneal epithelium defect/erosion, vitritis, uveitis, iritis, iridocyclitis, anterior chamber flare. Consult the SmPC in relation to other side effects. Overdose: Monitor intraocular pressure and treat if required. Incompatibilities: Do not mix with other medicinal products. Special Precautions for Storage: Store in a refrigerator (2°C to 8°C). Do not freeze. Unopened vials may be kept at room temperature (below 25°C) for up to 24 hours before use. Legal Category: POM. Package Quantities & Basic NHS Costs: Single vial pack £81.00. MA Numbers(s): EU/1/12/797/002. Further information available from: Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA, United Kingdom. Telephone: 01635 563000. Date of preparation: March 2015. Eylea® is a trademark of the Bayer Group

References (continued)