Management of Retinal Disease:

Advances in Treatment and Clinical Practice

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The 3rd Global Retinal Network Program Annual Meeting

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The 3rd annual meeting of the Global Retinal Network Program, an educational initiative developed by Bayer to foster scientific exchange and dialogue, attracted more than 350 delegates from 31 countries. A faculty of international retina specialists reviewed and debated current knowledge, shared clinical experience and considered practical approaches for achieving and maintaining optimal outcomes in the management of patients with retinal disease.

This supplement has been produced on behalf of Bayer and reports the Bayer-funded and organised 3rd Global Retinal Network Program Annual Meeting, May 20–21, 2017, Lisbon, Portugal. Attributed comment and opinion reflect the views of faculty speakers and participants and do not necessarily reflect those of Bayer. Prescribing information can be found on the last page.

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DME, diabetic macular edema; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor.

Plenary session I: The nature of retinal diseases

The underlying mechanisms of retinal diseases

The underlying mechanisms of retinal diseases and mode of action of intravitreal antiangiogenic therapies were reviewed by Mr Richard Gale, The York Hospital, York, UK. These considerations are believed to be especially helpful when comparing across anti-vascular endothelial growth factor (anti-VEGF) treatments and considering how these agents are best administered, remarked Mr Gale.

Hypoxia in the retina leads to the upregulation of cytokines, inflammatory mediators and growth factors such as VEGF, placental growth factor (PGF) and interleukin-6 (IL-6) (1, 2). The pathogenesis of diabetic macular edema (DME) and retinal vein occlusion (RVO) is associated with increased levels of VEGF, PGF and inflammatory factors (2–4). Intraocular VEGF and PGF levels increase with severity of RVO and diabetic retinopathy (DR), and are elevated in ischemic retinal vascular diseases (2–4). Aflibercept (Eylea®, Bayer) provides rapid and sustained gains in visual acuity (VA) in both ischemic and non-ischemic RVO and significantly reduces the severity of DR compared with sham intravitreal injections in clinical trials (5,6).

In vitro assessments show that intravitreal aflibercept blocks VEGF-induced activation of VEGF receptor 1 and 2 (VEGFR-1/-2) with 71 times greater potency than ranibizumab (Lucentis®, Novartis) (7). Aflibercept showed a mean VEGF-A suppression duration of 67 days compared with 34 days for ranibizumab in a study of treatment-naïve neovascular age-related macular degeneration (nAMD) eyes (8). Unlike ranibizumab, aflibercept also inhibits the activity of PGF. Inhibiting VEGF and PGF is believed to be more effective than inhibiting VEGF alone (3).

Mr Gale considered translation of these findings to clinical evidence and practice settings. The pivotal randomized, active-controlled phase III VIEW studies show that aflibercept given every 8 weeks after three initial monthly injections (2q8) and ranibizumab every 4 weeks were equally effective over 52 weeks in treatment-naïve nAMD (9)*. Through year 2, after a switch to a capped pro re nata (PRN, as-needed) regimen, the proportion of patients maintaining VA (losing <15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) remained stable across treatment groups (10). Close to half (48 percent) of patients treated with aflibercept 2q8 in year 1 were maintained on no more than quarterly dosing in the second year (11).

A prospective 2-year clinical trial in 40 treatment-naïve nAMD patients managed using a treat-and-extend regimen of aflibercept found that 75 percent achieved a treatment interval of 8 weeks or longer at the end of the year 2 visit. The median visual gain was 7.5 letters at 2 years from a median baseline of 59.0 letters and the mean number of injections was 8.0 and 6.5 during the first and second year, respectively (12). A separate study examined treatment extension in a population of refractory or recurrent nAMD patients switched to aflibercept; the switch resulted in stabilized VA and improved anatomic outcomes through a mean follow-up of 18 weeks (13).

A focus on nAMD: early diagnosis and prompt proactive treatment in year 1

Early diagnosis of nAMD and prompt access to anti-VEGF treatment is required for optimal treatment outcomes, as delay between indication to treat and treatment leads to irreversible VA deterioration, explained Mr Ian Pearce, Royal Liverpool University Hospital, Liverpool, UK (14, 15).

"We must promptly initiate anti-VEGF treatment of nAMD patients at the earliest opportunity when indicated, as baseline VA and lesion size are critical predictors of later vision," said Mr Pearce. "Other baseline predictors for VA outcomes in nAMD are presence of intraretinal cystoid fluid, elevation of the retinal pigment epithelium (RPE), foveal thickness, presence of retinal angiomatous proliferation (RAP) lesions and age" (14).

Clinicians must also remember to initiate treatment properly with the most appropriate loading phase and maintain continuation treatment with a proactive dosing regimen, stressed Mr Pearce. Neovascular AMD patients who receive an initial loading phase of anti-VEGF treatment (first three injections within 90 days) show greater improvements in VA than those who do not (Figure 1) (16, 17).

After the initial loading phase of 3 monthly anti-VEGF injections, follow-up dosing regimens may be fixed, proactive or reactive. Mr Pearce described studies of clinical effectiveness in clinical practice showing that good real-world outcomes can be achieved using the licensed aflibercept posology of fixed repeat dosing for nAMD in the first year of treatment (18, 19).

Twelve-month results of PERSEUS, a prospective, observational study involving 66 centers in Germany, show rapid and sustained visual gains with aflibercept for nAMD, with better visual outcomes observed in patients who received 3 monthly loading doses followed by bimonthly retreatment than those not receiving the full recommended induction course (mean VA improvement of 8.0 letters and 32 percent gaining ≥15 letters vs. mean VA improvement of 4.0 letters and 27.7 percent gaining ≥15 letters, respectively) (19).

Mr Pearce concluded with three main messages for clinicians: treat early, load effectively (on treatment initiation) with three initial monthly injections and then treat proactively with a fixed rather than a reactive PRN regimen through the first year for nAMD. Real-world outcomes similar to those seen in pivotal randomized clinical trials can be achieved using the licensed treatment posology for aflibercept in nAMD.

A focus on DME: early diagnosis and intensive treatment in year 1

The global prevalence of diabetes has doubled since 1980 (20). Diabetic eye disease is a leading cause of vision loss worldwide and the future burden of vision-threatening DR (proliferative DR [PDR] and/or central-involved DME) is expected to substantially increase as prevalence rates of diabetes rise further (21). Of 191 million people predicted to be affected by DR by 2030, 56 million will face sight-threatening PDR and/or central-involved DME, the latter being a major cause of sight loss in working-age adults (21, 22).

Regular screening of patients with diabetes is therefore essential to reduce the risk of sight loss due to DR, explained Dr Figen Şermet, Ankara University School of Medicine, Ankara, Turkey. Eye complications affect the ability of patients to manage their diabetes and other related complications (23). Global survey results from the DR Barometer Study show that more than a quarter of patients have never discussed eye complications with their doctor or did so only after symptoms arose and two-thirds of specialists reported that most of their diabetic patients only attend screening after vision problems arise (23).

There is a need to raise awareness of diabetic eye disease among general physicians and patients to promote early diagnosis and treatment, noted Prof Şermet (23,24). Additionally, a multidisciplinary team approach is encouraged to ensure broader communication between healthcare professionals involved in the management of people with diabetes (24).

Irreversible vision loss from diabetic eye disease may occur if treatment is delayed, Dr Şermet explained (25). VA at time of treatment initiation is associated with the visual outcome at 1 year in DME patients treated with intravitreal anti-VEGF therapy (26). Eyes with poorer VA at baseline are less likely to reach near normal VA (≥74 letters, ~Snellen equivalent 20/32 or better). Moreover, clinical trial data show better vision outcomes when DME patients are treated initially with anti-VEGF therapy compared with deferred treatment after initial laser treatment. Both issues demonstrate the importance of early diagnosis and treatment, said Dr Şermet.

As shown by the phase III RISE and RIDE trials of ranibizumab in DME, chronic retinal edema may result in some potential vision gain being irreversibly lost if left untreated (27). In the phase III VIVID-DME and VISTA-DME studies, which compared aflibercept with macular laser photocoagulation for DME, patients treated with laser control who then received aflibercept after week 100 achieved only modest vision gains thereafter (Figure 2) (25).

DME requires an intensive series of consecutive monthly doses on initiation of anti-VEGF therapy and continued regular retreatment in the first year, stressed Prof Şermet. Data show that DME patients continue to show improvement in VA and central retinal thickness (CRT) following the fourth and fifth initial monthly anti-VEGF loading doses (28). This is reinforced in the licensed posology for aflibercept for visual impairment due to DME: treatment initiation with one injection per month for five consecutive doses, followed by one injection every two months. After the first 12 months, the treatment interval may be extended, such as with a treat-and-extend dosing regimen.

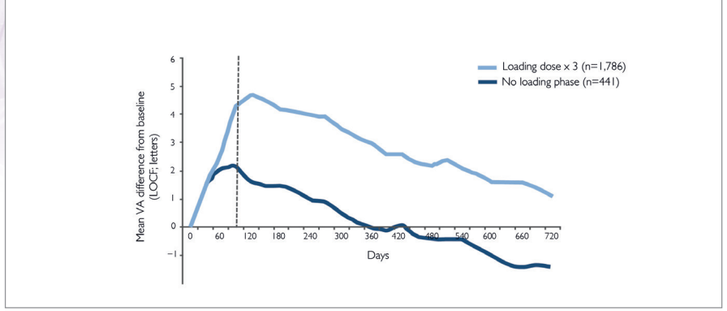


Figure 1. The importance of anti-VEGF loading doses in clinical practice: The AURA Study. AURA collected 'real-world' data in eight countries (Canada, France, Germany, Ireland, Italy, Netherlands, UK, and Venezuela) on clinical management patterns and resource utilization from 2,227 nAMD patients treated with ranibizumab. Patients who received three initial loading doses (first three injections within 90 days) showed greater improvements in VA vs. those who did not. The rate of decline in VA thereafter did not seem to be associated with administration of loading doses. LOCF, last observation carried forward; nAMD, neovascular age-related macular degeneration; VA, visual acuity; VEGF, vascular endothelial growth factor. Adapted from FG Holz et al., Br J Ophthalmol, 99, 220–226 (2015).

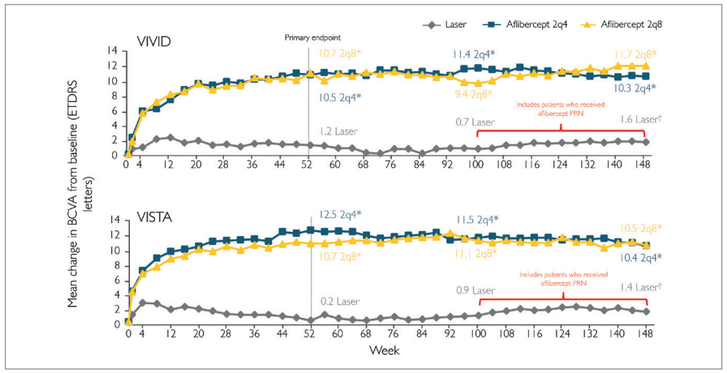


Figure 2. Results of VIVID and VISTA through 148 weeks. In the primary analysis, after week 100, patients in the laser group were eligible to receive aflibercept PRN. *P<0.0001 vs. laser. †Includes patients who received intravitreal aflibercept PRN from Week 100 to Week 148. Full analysis set; LOCF. VIVID-DME: Laser n=132; 2q4 n=136; 2q8 n=135. VISTADME: Laser n=154; 2q4 n=154; 2q8 n=151. 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks, following 5 initial monthly doses; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; LOCF, last observation carried forward; PRN, pro re nata (as needed); VEGF, vascular endothelial growth factor. Adapted from JS Heier et al., Ophthalmology, 123, 2376–2385 (2016).

*The dosing regimen for ranibizumab used in the VIEW trial programme does not represent its current UK posology, which can be found in its Summary of Product Characteristics [Lucentis® Summary of Product Characteristics (SmPC): https://www.medicines.org.uk/emc/medicine/19409].

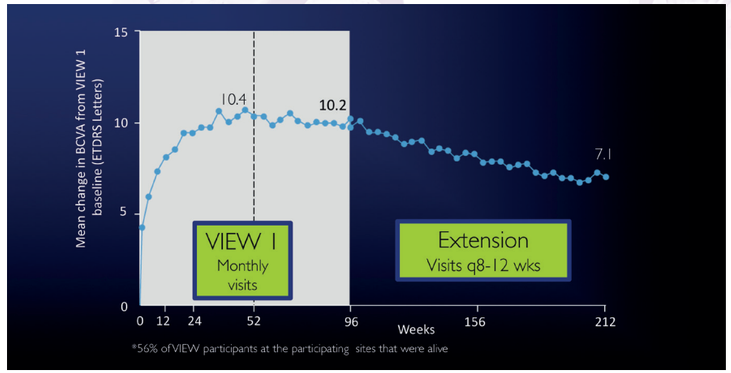


Figure 3. Results from the VIEW 1 extension study (33). Results are for 323/1217 (26.5 percent) of VIEW 1 participants (56 percent of VIEW participants at the participating sites that were alive). The results suggest subtle deterioration in VA when visit frequency is reduced despite capped PRN regimen at 8–12 weeks. ETDRS, Early Treatment Diabetic. Retinopathy Study; PRN, pro re nata; VA, visual acuity.

Management of DME and nAMD in year 1 and beyond

Evidence supporting recommended management strategies for DME and nAMD in year 1 and beyond was discussed by Dr Susan B Bressler, The Julia G. Levy, PhD Professor of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University School of Medicine & Hospital, Baltimore, MD, USA.

"We benefit from a wealth of data from randomized clinical trials showing that anti-VEGF therapy is effective in producing favorable vision outcomes in center-involving DME," noted Dr Bressler (25, 27, 29, 30). "Unlike nAMD, DME may have a finite, more circumscribed life cycle. But as with nAMD, an aggressive treatment approach with anti-VEGF therapy during the first year maximizes long-term vision gains, while monitoring intervals thereafter may be relaxed over time when VA and anatomic outcomes stabilize."

The Protocol I study from the Diabetic Retinopathy Clinical Research Network (DRCR.net) demonstrated that improvements in VA and retinal thickness obtained with anti-VEGF treatment, with immediate or deferred laser, are sustained over time in eyes with DME involving the central macula (30). Dr Bressler said there is a rapid ascent in VA letter score from baseline after the first series of monthly anti-VEGF injections and a continuing benefit seen between months 6 and 12. Considering both optical coherence tomography (OCT) retinal thickness and VA improvement (≥20/20 VA), initial responder rates increase with each successive injection during commencement of initial monthly dosing. This shows that the commitment to at least 5 monthly loading injections on treatment start is beneficial, observed Dr Bressler.

Vision and anatomic outcomes may be maintained through 5 years, with a strict loading phase of five or more injections and a structured retreatment protocol thereafter (30). The injection burden dramatically decreases after year 1 and even more so in years 4 and 5, without jeopardizing outcomes.

In contrast to DME, nAMD most often is an unremitting lifelong disease, added Dr Bressler. A continuing proactive treatment approach is needed for nAMD in year 1, for example using a fixed dosing regimen, and throughout the patient's therapeutic course. She recounted evidence from multiple long-term studies that diligent clinic follow-up and higher retreatment frequency are associated with better VA outcomes than often seen with variable as-needed dosing regimens (31, 32).

Seven-year outcomes in ranibizumab-treated patients (n=65) from the SEVEN-UP multicenter cohort study showed that at this late stage in the therapeutic course, exudative AMD patients remain at risk for substantial visual decline (31). At 5 years in the CATT Research Group Follow-Up Study, there was a mean change in VA from baseline of -3 letters, with the mean VA gain of 11 letters at 2 years being lost following a switch to retreatment based on best medical judgement (32).

Recent published data from the VIEW 1 Extension Study demonstrate long-term maintenance of VA gains through 4 years of continued aflibercept treatment, with a final mean VA improvement from baseline of 7.1 letters compared with a 10.2-letter gain at week 96 in the aflibercept 2q8 group (33).

"Frequent clinic attendance for regular assessment and monitoring of exudative nAMD activity is critical to maintain the very best level of VA for nAMD patients," explained Dr Bressler. "Continuous long-term retreatment generally maintains the success achieved in the first year with anti-VEGF treatment."

Impact of retinal disorders: a patient perspective

Impairment of vision has a significant impact on quality of life of patients, affecting both physical and mental health, observed Professor Bora Eldem, Hacettepe University, Ankara, Turkey (34, 35).

Patients are burdened by the impact of vision loss on their daily life and the resources needed for eye clinic visits. Quality-of-life loss associated with AMD can be devastating. Very severe AMD (VA ≤20/800) caused a 60 percent decrease in the average AMD patient's quality of life, similar to that encountered with end-stage prostate cancer or a catastrophic stroke (35). Mild AMD, defined as VA of 20/20 to 20/40 in the better-seeing eye, is associated with a greater quality-of-life decrement than that encountered with cancer, mild stroke, impotence or gout. Patients reported an average time per clinic visit of almost 12 hours, in a prospective, observational study of disease burden in the treatment of nAMD (36).

Prof Eldem cited findings illustrating that 5-letter gains of VA in both DME and nAMD patients provide relevant improvements in visual functioning performance.

Visual improvement of 5 letters or more in best corrected visual acuity (BCVA) was associated with important and measurable benefits for patients with DME, from an analysis of patient data up to week 52 from the VIVID and VISTA studies (37). Those patients with a 5-letter difference in BCVA in either the better- or worse-seeing eye were significantly more likely to be able to read print, drive at night and drive in difficult conditions (37). Clinically meaningful improvements in visual function outcomes, measured using the National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) composite score, were observed only in those nAMD patients who gained 5 ETDRS letters or more over 52 weeks with aflibercept 2q8 or monthly 0.5q4 ranibizumab in the VIEW studies (38).

Plenary session II: Insights in retinal disease management

Maximizing the use of OCT

Advances in OCT technology have provided a better understanding of retinal disease pathogenesis, with spectral domain OCT used predominantly for monitoring of progression and treatment response, explained Mr Gale (39).

Monitoring using OCT also enables earlier diagnosis and hence prompt access to treatment. Moreover, visualizing the extent and location of retinal fluid accumulation can provide insights into disease stage in eyes with nAMD (40). Topographical location, quantification of severity and morphological patterns of neovascularization and edema in the retina are useful predictors of treatment response in typical nAMD and DME (41–43).

In routine clinical practice, the main application of OCT in managing patients with nAMD is the qualitative assessment of features associated with choroidal neovascularization (CNV), including intraretinal fluid, subretinal fluid, elevation of the retinal pigment epithelium (RPE) and subretinal hyperreflective material (SHRM).

OCT allows clinicians to evaluate morphological changes to help guide anti-VEGF treatment regimens. Almuhtaseb et al. reported a mean VA gain of 8 ETDRS letters at month 11 in 223 patients receiving fixed dosing aflibercept for nAMD, with the macular status after loading shown to be a reliable indicator of disease activity at the end of the first year (18).

Emerging technologies such as OCT-Angiography (OCT-A) as well as ultra-widefield retinal imaging may provide further insights into disease pathogenesis beyond that detected by standard OCT alone and may impact routine practice in the years ahead (44). Mr Gale argued that OCT-A should be considered a complementary diagnostic tool alongside established imaging modalities. Ultra-widefield imaging allows peripheral retina assessment for disease screening, diagnosis and treatment, particularly for processes that are prevalent outside the traditional 7-fields (44).

Automated retinal image assessment represents a potentially valuable additional screening tool for retinal disease that may help to improve patient access to treatment and ease pressures on clinic resources (45). Several commercially available Automated DR Image Assessment Systems (ARIAS) have been found to provide efficient and cost-effective detection of referable retinopathy from digital fundus images, with acceptable sensitivity and sufficient specificity when compared to human graders (46).

Aflibercept across the retinal disease spectrum

Dr Susan B Bressler reviewed efficacy outcomes of aflibercept therapy across the retinal disease spectrum of nAMD and polypoidal choroidal vasculopathy (PCV), DME and retinal venous occlusive disease.

- VIEW nAMD studies and PLANET PCV study

Dr Bressler said the landmark VIEW studies set the stage for aflibercept therapy across the retinal disease spectrum. The VIEW 1 and VIEW 2 clinical trials demonstrated that aflibercept therapy dosed monthly and bimonthly after three initial monthly doses was as effective as ranibizumab given monthly over 52 weeks for treatment-naïve nAMD (9). All treatment groups were equally effective in improving BCVA and preventing BCVA loss at 96 weeks, the improvements in VA, CRT and CNV size during the first year generally sustained using capped PRN retreatment in the second year (Figure 3) (10).

More recently, the PLANET study (47) provided evidence that aflibercept monotherapy has been shown to be as safe and effective as aflibercept plus photodynamic therapy in patients with PCV. Mean change in VA from baseline to week 52 in the aflibercept monotherapy and aflibercept plus photodynamic therapy (PDT) arms was +10.7 letters and +10.8 letters, respectively, the 2-line gain with aflibercept monotherapy similar to that observed for typical AMD (47). Of note, VA outcomes in PCV patients at 12 months in the EVEREST II study reveal that ranibizumab in combination with PDT was superior to ranibizumab alone as assessed by mean VA gain from baseline (8.3 and 5.1 letters, respectively) (48).

- 148-week results of VIVID and VISTA

In VIVID and VISTA, aflibercept every 4 weeks (2q4) and aflibercept 2q8 resulted in better vision and anatomic outcomes than laser treatment in patients with visual impairment from central-involved DME at 1 year (6). Visual improvements observed with both aflibercept regimens over laser control at weeks 52 and 100 were maintained at week 148 (25). Mean BCVA gain from baseline to week 148 with aflibercept 2q4, aflibercept 2q8, and laser control was 10.3, 11.7 and 1.6 letters ($P < 0.0001$) in VIVID and 10.4, 10.5 and 1.4 letters ($P<0.0001$) in VISTA, respectively (25). From week 100, laser control patients who had not required rescue treatment received aflibercept as needed per retreatment criteria, but visual gains through the following 48 weeks were limited (25).

Figure 4. VA gains in aflibercept-treated patients. The majority of aflibercept-treated patients had significant VA gains (>15 letters), which were maintained up to 100 weeks. *AFL 3x2q4 then 2q8 if rescue criteria are met. **AFL PRN from Week 24 onwards. ***AFL PRN from Week 52 onwards. 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; AFL, aflibercept; PRN, pro re nata; VA, visual acuity. Adapted from JS Heier et al., Ophthalmology, 121, 1414–1420 (2014); Y Ogura et al,. Am J Ophthalmol, 158, 1032–1038 (2014); S Sivaprasad et al., Poster presentation, COPHy, Sorrento, Italy, March 26–29 (2015); DM Brown et al., Am J Ophthalmol, 155, 429–437 (2013); FG Holz et al., Br J Ophthalmol, 97, 278–284 (2013).

- COPERNICUS, GALILEO and VIBRANT studies evaluating aflibercept in RVO

Results of COPERNICUS, GALILEO and VIBRANT clinical trials show that the majority of aflibercept-treated RVO patients had significant VA gains from baseline (≥15 letters) that were maintained up to 100 weeks (vs. laser or sham treatment) (Figure 4) (49, 51). Between 52 and 60 percent of RVO patients gained 3 or more lines of vision after 24 weeks of aflibercept treatment, which was sustained at 52 weeks and beyond. The percentage of perfused (fewer than 10 disc areas of non-perfusion) patients increased with aflibercept therapy. In BRVO patients in VIBRANT, the percentage of perfused patients in the laser arm remained relatively stable and increased after aflibercept rescue therapy became available from week 24 (51).

Real-world evidence of anti-VEGF treatment outcomes

Randomized clinical trials often lack generalizability as they are conducted in well-defined patient populations using a standardized care protocol. In a shift of focus from clinical trial data to clinical practice, Mr Pearce reviewed real-world evidence of treatment effectiveness with the use of anti-VEGF agents for nAMD.

Prospective and retrospective studies demonstrate that nAMD patients treated less frequently tend to lose initial vision gains achieved with fixed and typically more frequent dosing, noted Mr Pearce. Results from the UK nAMD Database Study of real-life outcomes of PRN ranibizumab (following loading with 3 monthly injections) in treatment-naïve nAMD show worse visual outcomes than those obtained in the registration randomized controlled clinical trials (52). Mean VA (letters) change from baseline at years 1, 2 and 3 was +2, +1 and -2, respectively. The median number of treatments for eyes followed for at least 3 years in years 1, 2 and 3 was 5, 4, and 4, respectively, a substantially lower dosing frequency than the monthly dosing regimen followed in the pivotal ranibizumab randomized clinical trials.

Poor VA outcomes in clinical practice seem to relate largely to undertreatment with anti-VEGF therapy, observed Mr Pearce, who acknowledged there are limitations to how often patients can be monitored in eye clinics. Maintaining a sufficient frequency of anti-VEGF injections is nevertheless important for achieving optimal gains in VA over time (16). The AURA multicountry observational study reported greater improvements in VA in those countries delivering a higher frequency of both anti-VEGF treatments and clinic visits over 2 years (16, 53).

Good outcomes may be achieved and maintained when following the licensed treatment posology for aflibercept in the first year, illustrated by growing evidence from multiple countries and across diverse patient populations, Mr Pearce observed (Figure 5).

A large multicenter, national Electronic Medical Record (EMR) study compared the effectiveness of predominantly PRN ranibizumab versus continuous (fixed or treat-and-extend) aflibercept therapy in UK clinical practice, involving 1,884 eyes across 21 UK hospitals (54). At one year, patients treated with PRN ranibizumab (average of 5.8 injections) gained 1.6 letters from baseline compared with a mean improvement of 6.1 letters for patients receiving fixed or treat-and-extend aflibercept (7.0 injections). The adjusted difference in change of vision at 1 year was 4.1 letters (P<0.0001) in favor of continuous aflibercept (Figure 6).

Data from RAINBOW, an ongoing retrospective and prospective 4-year observational study in France evaluating real-life outcomes in treatment-naïve nAMD patients treated with aflibercept, illustrate the importance of the loading phase. For patients treated with a loading phase of 3 injections within 90 days (n=284, mean baseline BCVA ± SD 57.2±17.8), mean change in BCVA from baseline to month 12 was +6.8±14.5 letters, with a mean of 6.6±1.8 injections, compared with a mean change of +5.5±15.0 letters and a mean of 6.0±2.1 injections for all patients (n=353, mean baseline BCVA 57.7±17.8) in the full analysis cohort (17).

After year 1, initial VA gains may be maintained using a treat-and-extend dosing regimen, added Mr Pearce. Epstein and Amrén reported maintenance of the 12-month VA improvement of 7.2 letters at the 18-month visit following a switch from fixed to treat-and-extend dosing in 85 nAMD patients (55). Approximately two injections were given in the final 6 months.

Mr Pearce concluded: "Collecting real-world evidence of effectiveness helps benchmark performance to improve standards of care and treatment patterns in clinical practice. In real life, a proactive treatment regimen for nAMD appears to be the most successful approach to vision improvement and preservation of VA gains. After year 1, treatment intervals with aflibercept may be extended in some patients using treat-and-extend dosing, stabilizing VA gains long-term while decreasing treatment frequency and clinic visits" (57).

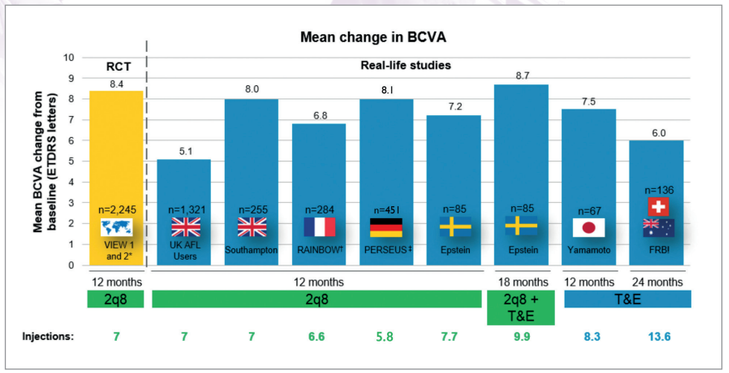


Figure 5. Selected studies of real-world evidence of aflibercept in nAMD. NB. Figure contains data from different studies and is for information only; no direct comparisons should be made. *Data from the aflibercept 2q8 arm (following 3 initial monthly loading doses). †Data included are from patients treated with a loading phase. ‡Data included are from patients treated according to posology. 2q8, 2 mg every 8 weeks; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration; RCT, randomized controlled trial; RWE, real-world evidence; T&E, treat-and-extend. Adapted from U Schmidt-Erfurth et al., Ophthalmology, 121, 193–201 (2014); M Weber et al., Oral presentation, Congress of the Société Française D'Ophtalmologie; Paris, France, May 6–9, 2017; H Almuhtaseb et al., Eye (Lond) [Epub ahead of print] (2017); C Framme and L Kodjikian. Presentation at ARVO 2017, Baltimore, MD, USA, May 7–11 (2017); D Epstein and U Amrén. Retina, 36, 1773–1777 (2016); A Yamamoto et al., Ophthalmologica, 237, 139–144 (2017); JS Talks et al., Ophthalmology, 123, 337–343 (2016); N Eter et al., Presentation at ARVO 2017, Baltimore, MD, USA, May 7–11 (2017).

Treatment options in DME: the role of anti-VEGF agents, laser and steroids

Dr Neil Bressler, Wilmer Eye Institute, Johns Hopkins University School of Medicine and Hospital, Baltimore, MD, USA, explored treatment options for DME, emphasizing that completed DRCR.net studies provide robust evidence of the superiority of anti-VEGF therapy over both laser or corticosteroid therapy for the initial management of center-involved DME with vision loss.

Results from DRCR.net Protocol I show that ranibizumab with prompt or deferred laser was more effective than laser for central-involved DME (58). Overall, improvement in VA at 1 year with ranibizumab was maintained at 5 years alongside a diminishing need for retreatment over time (30). Longer-term assessment also confirmed that combining laser at initiation of ranibizumab treatment was no better than deferring laser at least by 24 weeks (30). The observed difference in VA in favor of deferred laser may be related to the greater number of ranibizumab injections during follow-up or the potentially destructive effect of prompt laser.

For a DME patient with diminished VA of 20/63 and a central subfield thickness of 462 µm, Dr Bressler recommended commencement of anti-VEGF treatment with 5 to 6 initial monthly doses, securing continuing improvements in anatomic and visual response with each consecutive dose. For a patient with persistent DME after this induction phase and beyond, clinicians may consider adding focal/grid laser and resume anti-VEGF treatment only if outcomes worsen.

Dr Bressler said there is some evidence of harm following cataract surgery in eyes with central-involved DME and persistent edema and argued that corticosteroids should be avoided in phakic patients as they will cause cataract progression. DRCR.net Protocol P found that 40 percent of eyes with DME undergoing cataract surgery had no meaningful improvement or had worsening of VA and 53 percent of eyes had a VA of ≤20/40 at the 16-week postoperative visit (59). Even in pseudophakic eyes there is no rationale to support starting treatment with steroids rather than anti-VEGF therapy, argued Dr Bressler.

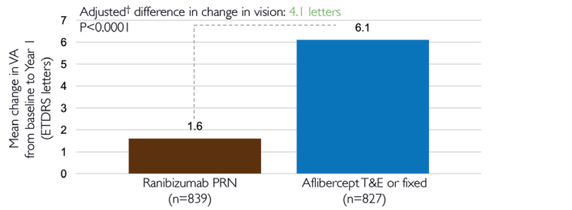
The role of switching to corticosteroids in pseudophakic patients with persistent edema despite initial anti-VEGF therapy is not yet known. DRCR.net Protocol U will assess short-term efficacy outcomes at 24 weeks of combination corticosteroid (dexamethasone implant [Ozurdex®, Allergan]) and anti-VEGF treatment (ranibizumab) in comparison with continued anti-VEGF monotherapy in eyes with persistent central-involved DME and VA impairment despite previous anti-VEGF therapy, in both pseudophakic and phakic patients.

Clinician debate on the role of laser in DME

Dr Hazem El-Sabagh, Magrabi Eye Center, Dammam, Saudi Arabia, said laser may be an effective primary treatment option for some patients with DME (60). Considerations include compliance, contraindications (e.g., pregnancy), cost or exhaustion of health budget and morphological signs of recalcitrant or chronic persistent edema. Focal laser treatment can maintain vision and reduce retinal thickness in some patients with non-center-involved DME and achieves similar outcomes to steroid treatment in DME but with fewer side effects (60–62).

DME patients should be treated first-line with anti-VEGF agents to ensure maximal treatment outcomes, argued Mr Igor Kozak, Moorfields Eye Hospital Center, Abu Dhabi, United Arab Emirates, in a counterpart presentation (25, 63). He cited head-to-head comparative effectiveness studies showing that laser treatment is less efficacious than anti-VEGF therapy in improving vision in DME patients (25, 63).

Ranibizumab 0.5 mg treatment for 12 months either as monotherapy or as an adjunct to laser therapy produced



At 1 year:	Ranibizumab	Aflibercept	P-value
Average number of injections	5.8	7.0	P<0.0001
Average number of clinic visits	10.8	9.0	P<0.0001

Figure 6. Data from 21 UK centers. Multicenter data analysis from EMR systems of 1,884 eyes with treatment-naïve nAMD who received ranibizumab PRN or aflibercept (fixed bimonthly dosing or treat-and-extend). Both ranibizumab and aflibercept were administered after three initial monthly loading doses. Significantly greater vision gains were achieved at year 1 with aflibercept compared with ranibizumab. Please note that some patients in the aflibercept arm received an off-label posology of aflibercept. Bayer recommends the use of its products in accordance with licensed posology – please refer to your local summary of product characteristics for details.

*Following 3 initial monthly loading doses. †Adjusted for age, gender, starting year and starting VA at 1 year. EMR, electronic medical record; ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration; PRN, pro re nata (as needed); T&E, treat-and-extend; VA, visual acuity. Adapted from AY Lee et al., Br J Ophthalmol [Epub ahead of print] (2017).

significantly greater improvements in BCVA and CRT than laser treatment alone in the randomized, laser-controlled RESTORE study (63). The DRCR.net Protocol I study showed that patients treated with laser at baseline achieved poorer visual outcomes than those treated with deferred laser (Figure 7) (30). In VIVID and VISTA, visual and anatomic improvements as well as improvements in Diabetic Retinopathy Severity Scale (DRSS) score with macular laser photocoagulation were inferior to those with aflibercept therapy (25, 64). Over 80 percent of patients in the laser control groups required additional treatment with aflibercept (25).

Scarring remains a side effect of laser treatment despite technology advances, added Mr Kozak. The underlying mechanism of action of laser treatment in DME is unknown and, despite several decades of use, the optimal protocol for subthreshold laser photocoagulation is unclear. For these reasons, laser should not be used first-line for the treatment of DME.

Clinician debate on the role of steroids in DME – the speakers' opinions

Corticosteroids may be prescribed for persistent DME that is unresponsive to alternative treatments and there may well be opportunities to use steroids as first-line therapy for DME, commented Professor Ângela Carneiro, Faculty of Medicine of University of Porto, Centro Hospitalar São João, Porto, Portugal. Intravitreal steroid treatment is a feasible first-line option for central-involved DME in patients who are pseudophakic, who are unable to adhere to a more intensive treatment regimen, have experienced prior or recent arterial thromboembolic events and in patients for whom anti-VEGF treatment is not reimbursed (65–67). Increased intraocular pressure (IOP) with steroid treatment can be clinically relevant in one-third of patients but can often be controlled by medical therapy, added Prof Carneiro.

A person with central-involved DME considered unsuitable for initial anti-VEGF therapy may not necessarily be suitable for first-line steroid therapy, countered Mr Pearce. Longer retreatment intervals with steroids are negated by the requirement for regular monitoring of IOP. Furthermore, vision gains with steroid therapy are not maintained long term. Peak vision gains occur approximately 2 months after dexamethasone implant injection, followed by regression toward baseline (65, 67). Moreover, the risk of visual loss from uncontrolled central-involved DME far outweighs any theoretical risk of serious systemic adverse events with intravitreal VEGF inhibitor therapy.

Guideline recommendations from EURETINA

Guidelines from the European Society of Retina Specialists (EURETINA) confirm that laser treatment is no longer the standard of care in the management of DME (68). Nonetheless, subthreshold grid laser treatment can be helpful in eyes with higher VA affected by early diffuse DME. Relative indications for laser treatment in DME include:

- laser application especially to the vasogenic subform of DME, which is clinically characterized by the presence of focally grouped macular edema and leaking capillaries;
- eyes affected by DME with CRT less than 300 µm or eyes with persisting vitreomacular adhesion, because comparable results can be achieved by means of laser photocoagulation or anti-VEGF injections (68).

Corticosteroids have maintained a role for chronically persistent DME and largely as a second choice intervention, according to EURETINA guidelines. In nonresponders previously treated with anti-VEGF therapy, it is reasonable to consider a switch to steroid therapy. The use of steroids may be considered as primary therapy in patients who have a history of major cardiovascular events, as these patients were excluded from all major ant-VEGF treatment trials, and in patients who are unwilling to attend for monthly injections (and/or monitoring) in the first 6 months of therapy. Because of the elevated risk for cataract surgery, pseudophakic patients are preferred for the use of steroids and the IOP has to be monitored frequently in all cases.

However, there is no established definition of nonresponse to initial anti-VEGF treatment, cautioned Dr Susan B Bressler. She explained there is no evidence from controlled studies showing that switching to alternative steroid treatment will alter outcomes beyond that of the initial intervention.

Clinical insights from plenary presentations and discussions

Dr Susan B Bressler reflected on the main clinical insights from plenary presentations and faculty discussions and presented take-home learning points:

- Cytokines other than VEGF-A may play a contributory role in the pathogenesis of common retinal diseases. Aflibercept has a higher binding affinity, longer duration of VEGF suppression and broader mechanism of action than other ophthalmic anti-VEGF therapies. It is the only intravitreal antiangiogenic agent at clinicians' disposal that inhibits both VEGF-A and PGF. These distinguishing molecular features may partly account for observed differences in clinical effectiveness from prospective and retrospective studies of different anti-VEGF agents in routine clinical practice.
- VA at baseline is an important predictor of later visual outcomes with continuing anti-VEGF therapy, underscoring the importance of early detection. When edema starts to encroach on the macular center, clinicians are encouraged not to delay proceeding to anti-VEGF treatment, as patients receiving deferred antiangiogenic therapy do not achieve the magnitude of vision improvement attained by prompt early treatment.
- The standard of care for the primary treatment of center-involved DME with vision loss is anti-VEGF therapy. Responder rates continue to increase with each successive dose through at least 5 monthly injections, so it is important not to undertreat during the mandated induction phase. While DME requires intensive initial treatment, there is potential for a decreased visit and treatment frequency in subsequent years.
- nAMD is a chronic condition requiring aggressive initial treatment early on and diligent proactive follow-up and retreatment for preservation of good visual outcomes long term. Treatment initiation with an adequate loading phase of initial monthly injections and continuing proactive treatment within the first year and beyond ensures maximal visual benefit longer term.
- Vision functioning outcomes reflect the beneficial effects of treatment from the patient's perspective. There is evidence of a correlation between level of ETDRS letter score improvement and improved ability to continue to perform everyday vision-related tasks.
- Advances in OCT imaging technology have provided greater insights into disease pathogenesis and OCT provides the ability to monitor key morphological features for assessment of objective change in response to treatment. Emerging and evolving technologies likely to impact clinical practice include OCT-A, ultra-widefield imaging and automated retinal image assessment for detection of referable retinopathy.
- Aflibercept monotherapy may be a reasonable option for the initial management of PCV without having to resort to adjunctive PDT in the vast majority of cases.
- Treatment outcomes of aflibercept in nAMD from clinical practice evaluations across multiple countries and clinic centers compare favorably to the visual and anatomic results observed in the pivotal phase III VIEW studies.
- Anti-VEGF therapy is superior to laser therapy or corticosteroids as initial treatment for center-involved DME with vision loss and has emerged as the preferred first-line treatment option. For center-involved DME without vision loss and for diffuse DME without central involvement, more evidence comparing careful observation with alternative treatment interventions is needed.

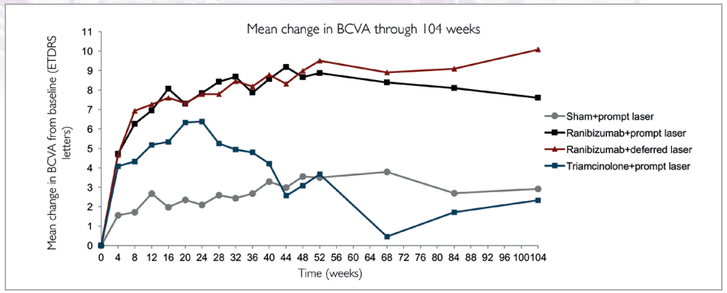


Figure 7. DRCR.net Protocol I: vision gains with steroids are not maintained long term. Initial vision gains were not maintained through 104 weeks. At week 104, the mean change in VA from baseline was signifcantly worse in the triamcinolone + prompt laser group than the sham + prompt laser group (-1.6 letters, p<0.001; triamcinolone is not licensed for the treatment of DME). BCVA, best corrected visual acuity; DME, diabetic macular edema; DRCR.net, Diabetic Retinopathy Clinical Research Network; ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity. Adapted from MJ Elman et al., "Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema", Ophthalmology, 6, 1064-1077.e35. (2010). PMID: 20427088

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Eylea® 40 mg/ml solution for injection in a vial (aflibercept) Prescribing Information
(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 1 ml solution for injection contains 40 mg aflibercept. Each vial contains 100 microlitres, equivalent to 4 mg aflibercept. **Indication(s):** Treatment of neovascular (wet) age-related macular degeneration (AMD), macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to diabetic macular oedema (DMO) in adults and visual impairment due to myopic choroidal neovascularisation (myopic CNV). **Posology & method of administration:** For intravitreal injection only. Must be administered according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. 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. Refer to SmPC for full details. ***Adults:*** The recommended dose is 2 mg aflibercept, equivalent to 50 microlitres. For wAMD treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two months. No requirement for monitoring between injections. After the first 12 months of treatment, and based on visual and/or anatomic outcomes, the treatment interval may be extended such as with a treat-and-extend dosing regimen, where the treatment intervals are gradually increased to maintain stable visual and/or anatomic outcomes; however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. The schedule for monitoring should therefore be determined by treating physician and may be more frequent than the schedule of injections. For RVO (branch RVO or central RVO), after the initial injection, treatment is given monthly at intervals not shorter than one month. Discontinue if visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment. Treat monthly until maximum visual acuity and/or no signs of disease activity. Three or more consecutive, monthly injections may be needed. Treatment may then be continued with a treat and extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes, however there are insufficient data to conclude on the length of these intervals. Shorten treatment intervals if visual and/or anatomic outcomes deteriorate. The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response. For DMO, initiate treatment with one injection/month for 5 consecutive doses, followed by one injection every two months. No requirement for monitoring between injections. After the first 12 months of treatment, and based on visual and/or anatomic outcomes, the treatment interval may be extended such as with a treat-and-extend dosing regimen, where the treatment intervals are gradually increased to maintain stable visual and/or anatomic outcomes; however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. The schedule for monitoring should therefore be determined by the treating physician and may be more frequent than the schedule of injections. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, treatment should be discontinued. For myopic CNV, a single injection is to be administered. Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists. Recurrences should be treated as a new manifestation of the disease. The schedule for monitoring should be determined by the treating physician. The interval between two doses should not be shorter than one month. ***Hepatic and/or renal impairment:*** No specific studies have been conducted. Available data do not suggest a need for a dose adjustment. ***Elderly population:*** No special considerations are needed. Limited experience in those with DMO over 75 years old. ***Paediatric population:*** No data available. **Contraindications:** Hypersensitivity to active substance or any excipient; active or suspected ocular or periocular infection; active severe intraocular inflammation. **Warnings & precautions:** As with other intravitreal therapies endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract have been reported. Aseptic injection technique essential. Patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Patients must report any symptoms of endophthalmitis or any of the above mentioned events without delay. Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection; special precaution is needed in patients with poorly controlled glaucoma (do not inject while the intraocular pressure is ≥ 30 mmHg). Immediately after injection, monitor intraocular pressure and perfusion of optic nerve head and manage appropriately. There is a potential for immunogenicity as with other therapeutic proteins; patients should report any signs or symptoms of intraocular inflammation e.g pain, photophobia or redness, which may be a clinical sign of hypersensitivity. Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors. Safety and efficacy of concurrent use in both eyes have not been systemically studied. No data is available on concomitant use of Eylea with other anti-VEGF medicinal products (systemic or ocular). Caution in patients with risk factors for development of retinal pigment epithelial tears including large and/or high pigment epithelial retinal detachment. Withhold treatment in patients with: rhegmatogenous 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 of ≥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. In patients presenting with clinical signs of irreversible ischaemic visual function loss, aflibercept treatment is not recommended. Populations with limited data: 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, or in diabetic patients with uncontrolled hypertension. This lack of information should be considered when treating such patients. In myopic CNV there is no experience with Eylea in the treatment of non-Asian patients, patients who have previously undergone treatment for myopic CNV, and patients with extrafoveal lesions. **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-foetal 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:* Visual acuity reduced, conjunctival haemorrhage (wet AMD phase III studies: increased incidence in patients receiving anti-thrombotic agents), eye pain. *Common:* retinal pigment epithelial tear (known to be associated with wet AMD; observed in wet AMD studies only), detachment of the retinal pigment epithelium, retinal degeneration, vitreous haemorrhage, cataract (nuclear or subcapsular), corneal abrasion or erosion, increased intraocular pressure, blurred vision, vitreous floaters, vitreous detachment, injection site pain, foreign body sensation in eyes, increased lacrimation, eyelid oedema, injection site haemorrhage, punctate keratitis, conjunctival or ocular hyperaemia. *Serious: cf. CI/W&P* - in addition: blindness, culture positive and culture negative endophthalmitis, cataract traumatic, transient increased intraocular pressure, vitreous detachment, retinal detachment or tear, hypersensitivity (during the post-marketing period, reports of hypersensitivity included rash, pruritus, urticaria, and isolated cases of severe anaphylactic/anaphylactoid reactions), vitreous haemorrhage, cortical cataract, lenticular opacities, corneal epithelium defect/erosion, vitritis, uveitis, iritis, iridocyclitis, anterior chamber flare, arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors. As with all therapeutic proteins, there is a potential for immunogenicity.
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 stored at room temperature (below 25°C) for up to 24 hours before use. **Legal Category:** POM. P**ackage Quantities & Basic NHS Costs:** Single vial pack £816.00. **MA Number(s):** EU/1/12/797/002. **Further information available from:** Bayer plc, 400 South Oak Way, Reading RG2 6AD, United Kingdom. Telephone: 0118 206 3000. **Date of preparation:** November 2017.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
Adverse events should also be reported to Bayer plc. Tel.: 0118 2063500, Fax.: 0118 2063703, Email: pvuk@bayer.com

UKEYL10170236. Date of preparation: March 2018.