Evaluation of Physician and Patient Knowledge of Safety and Safe Use Information for Aflibercept in Europe: An Observational Postauthorisation Study

Version 3.0

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Prepared for
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Country(-ies) of study	The United Kingdom, Germany, France, Spain, and Italy
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2 List of Abbreviations

AE	adverse event
AMD	age-related macular degeneration
ATC	Anatomical Therapeutic Chemical Classification System
BHC	Bayer HealthCare Pharmaceuticals, Inc.
CRVO	central retinal vein occlusion
DME	diabetic macular oedema
EC	ethics committee
EDC	electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres of Pharmacoepidemiology and Pharmacovigilance
GPP	good pharmacoepidemiology practices
GVP	good pharmacovigilance practices
INN	international nonproprietary names
IRB	institutional review board
PASS	postauthorisation safety studies
PVCH	BHC pharmacovigilance country head
RTI-HS	RTI Health Solutions
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
US	United States
VEGF	vascular endothelial growth factor
wAMD	wet age-related macular degeneration

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4 Abstract

Title

Evaluation of Physician and Patient Knowledge of Safety and Safe Use Information for Aflibercept in Europe: An Observational Postauthorisation Study

Rationale and Background

Aflibercept (Eylea) is a new compound administered as an intravitreal injection. Aflibercept is a fusion protein specifically designed to bind all forms of VEGF-A and placental growth factor, two proteins involved in the abnormal growth of new blood vessels (Regeneron Pharmaceuticals, Inc., 2010). Intravitreal injections, including anti-VEGF therapies, have been associated with some uncommon complications such as endophthalmitis, transient increases in intraocular pressure, glaucoma, cataract, and retinal and vitreous detachment.

Aflibercept (Eylea) has been approved by the European Medicines Agency (EMA) for the treatment of neovascular (wet) age-related macular degeneration (wAMD), visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO), and visual impairment due to diabetic macular oedema (DME). Age-related macular degeneration (AMD) is the leading cause of vision loss in older adults. Normally, vascular endothelial growth factor (VEGF) promotes the growth of collateral blood vessels and the restoration of damaged endothelium. Macula oedema secondary to CRVO is the second most common cause of visual loss from retinal vascular disease. CRVO may be the result of a number of factors including vein compression, hemodynamic disturbances, vessel wall changes, and blood changes. This damage can lead to increased secretion of VEGF, which can stimulate new vascular growth (which is responsible for secondary complications of CRVO). Several anti-VEGF therapies have shown promising results in treating CRVO macular oedema in comparison to other therapies. DME is an advanced complication of diabetic retinopathy, the most common microvascular complication of diabetes, and accounts for much of the vision loss associated with diabetic retinopathy. The chronic microvascular damage in this condition leads to increased intraocular secretion of VEGF. Aflibercept and other anti-VEGF therapies have demonstrated improvement in visual acuity in patients with DME and have largely replaced laser photocoagulation as the preferred treatment.

As part of the risk management plan for aflibercept, Bayer HealthCare Pharmaceuticals Inc. (BHC) has developed materials to help educate both physicians and patients on the key safety information and safe use for aflibercept. BHC has collaborated with RTI Health Solutions (RTI-HS) to develop an observational postauthorisation safety study. The purpose of this study will be to assess physician and patient knowledge and understanding of the key safety information in the aflibercept educational materials developed by BHC.

Research Question and Objectives

The primary objective of this study is to measure physician and patient knowledge and understanding of the key information contained in the aflibercept educational materials: the prescriber guide and video, and the patient booklet "Your guide to EYLEA," patient information leaflet, and audio CD.

Specifically, the following objectives will be addressed:

- Investigate whether physicians and their patients have received the educational materials
- Assess physicians' knowledge and understanding of key safety information contained in the prescriber guide and the intravitreal injection procedure video and assess how physicians use the materials in their daily practice
- Assess patients' knowledge and understanding of the key safety information contained in the patient booklet "Your guide to EYLEA," patient information leaflet, and audio CD and determine if the patients used this information.

Study Design

- The study will be an observational, cross-sectional study of knowledge, understanding, and self-reported behaviour among a sample of physicians and patients with recent aflibercept experience in a total of up to five European countries.
- Physicians will be recruited using a random sample of physicians (ophthalmologists) from a physician panel or list with the aim of obtaining a sample generally representative of the physicians in the selected countries who prescribe and administer aflibercept. Following consent, physicians will be asked to complete the questionnaire evaluating their knowledge and understanding of key safety information, as well as their receipt and use of the aflibercept educational materials.
- Patients who have received at least one injection with aflibercept will be recruited by their physicians and invited to participate in the study. The physicians selected for participation in the patient assessment will not be included in the physician assessment described above. Following consent, patients will complete an interviewer-administered questionnaire with closed-ended questions. The patient questionnaire will assess patients' knowledge and understanding of the key safety information in the aflibercept educational materials they have received.
- Data from the questionnaire responses will be analysed to ascertain the level of knowledge, understanding, and reported safe use practices among these physicians and patients, stratified by country and other relevant characteristics (e.g., number of prior injections).

Population

- Physicians eligible to participate will be ophthalmologists who have administered aflibercept in the past 6 months.
- Patients eligible to participate will be those who have already received at least one aflibercept injection and are returning for a subsequent visit. Patients will be aged 18 years or older, and will be able to understand the native language of the country in which the study is conducted.

Variables

- The physician questionnaire will contain questions eliciting responses measuring physician knowledge and understanding of the key information in the aflibercept prescriber guide and intravitreal injection procedure video.
- The patient questionnaire will contain questions eliciting responses measuring patient knowledge and understanding of the key information contained in the aflibercept patient booklet "Your guide to EYLEA," patient information leaflet, and audio CD.

Data Sources

The source of information for the study will be self-reported data collected from physicians and patients using standard questionnaires with primarily closed-ended response choices.

Study Size

- The physician assessment will target 60 to 100 participating physicians per country, for a total of 300 to 500 physicians overall, to allow reasonable precision around estimates of physicians' knowledge and understanding of the prescriber guide and intravitreal injection procedure video.
- The patient assessment will target up to 150 patients per country, for a total of up to 750 patients overall, to allow reasonable precision around estimates of patients' knowledge and understanding of the key information contained in the patient booklet "Your guide to EYLEA," patient information leaflet, and audio CD at the study level.

Data Analysis

Analyses will include detailed review of responses to individual questions as well as potential summary measure across logical grouping of response items. Physician results will be stratified by country and other logical variables. Patient results will be stratified by country and other logical variables, potentially including a measure of the knowledge level of their physician. A detailed analysis plan describing methods of analysis and presentation and including table shells will be developed before analysis of data is initiated. In addition to a description of the analysis of the questionnaire data, the analysis plan will describe any planned comparisons of participants and non-participants.

5 Amendments and Updates

Number	Date	Section of Study Protocol	Amendment or update	Reason
1	3 February 2015	4, 6, 7, 9, 10, 11	Amendment	Revisions were made to incorporate additional indications into the study, to increase the patient sample size, to update the mode of data collection for the patient questionnaire based on findings from cognitive testing, and to update the AE reporting process based on the new mode of data collection for patients. Minor editorial revisions were also made for clarity of text and the timeline was updated.

6 Milestones and Timeline

Milestone	Timeline
European Medicines Agency (EMA) approval of protocol and questionnaires	To be determined
Completion of cognitive pretesting of questionnaires	6 months from EMA approval of protocol and questionnaires
Submission for ethics committee (EC) review and approval	EC approval 6-8 months from finalization of protocol version 3.0
Registration in the EU PAS register	Prior to start of data collection
Completion of site recruitment, contracting, and training; start of data collection	3 months from EC approval
End of data collection	10 months from start of data collection
Completion of data analysis	2-4 months from end of data collection
Final report of study results	2-3 months from completion of data analysis
Study progress reports (to be submitted with Periodic Safety Update Reports)	Every 6 months throughout the study

7 Rationale and Background

Aflibercept (Eylea) is a new compound administered as an intravitreal injection. Aflibercept is a fusion protein specifically designed to bind all forms of VEGF-A and placental growth factor, two proteins involved in the abnormal growth of new blood vessels (Regeneron Pharmaceuticals, Inc., 2010). Intravitreal injections, including anti-VEGF therapies, have been associated with some uncommon complications such as endophthalmitis, transient increases in intraocular pressure, glaucoma, traumatic cataract, and retinal and vitreous detachment. The frequency of those complications associated with the use of intravitreal injections ranges from less than 1% to 2%. Less serious and more common complications include conjunctival hemorrhage, vitreous floaters, and eye pain (Csaky and Do, 2009; Jeganathan and Verma, 2009). Some reports based on exposure to the anti-VEGF therapies ranibizumab (Lucentis) and bevacizumab (Avastin) have noted the potential of such therapies to increase the risk of experiencing coronary heart disease, cerebrovascular disease, or both (Csaky and Do, 2009; Micieli et al., 2010).

Aflibercept (Eylea) has been approved by the European Medicines Agency (EMA) for the treatment of neovascular (wet) age-related macular degeneration (wAMD), visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO), and visual impairment due to diabetic retinal oedema (DME).

Age-related macular degeneration is the leading cause of vision loss in older adults. Normally, vascular endothelial growth factor (VEGF) promotes the growth of collateral blood vessels and the restoration of damaged endothelium. However, VEGF abnormally secreted in the eyes plays a major role in neovascular (wet) age-related macular degeneration (wAMD), in which new blood vessels grow beneath the retina and leak blood and fluid, disrupting retinal function and causing vision loss (Regeneron Pharmaceuticals, Inc., 2010). The prognosis of wAMD has improved markedly with the introduction of anti–vascular endothelial growth factor (anti-VEGF) therapies to prevent or ameliorate the vision loss associated with wAMD (Folk and Stone, 2010; Jager et al., 2008; Jeganathan and Verma, 2009; Regeneron Pharmaceuticals, Inc., 2010; Vedula and Krzystolik, 2008).

Retinal vein occlusion is the second most common cause of visual loss from retinal vascular disease, with the non-ischaemic type being more common and with better visual acuity prognosis than the ischaemic type. Classification of retinal vein occlusion includes three main groups depending on the location of venous occlusion: CRVO, branch retinal vein occlusion (BRVO), and hemiretinal vein occlusion (HRVO). Patients with CRVO have worse visual outcomes than patients with BRVO or HRVO. CRVO occurs due to thrombus within the central retinal vein, leading to involvement of the entire retina. The limited space in this area can predispose the central vein to thrombus formation and

other secondary damage. CRVO may be the result of a number of factors including vein compression, hemodynamic disturbances, vessel wall changes, and blood changes. This damage can lead to increased secretion of VEGF, which can stimulate new vascular growth and is responsible for secondary complications of CRVO. Neovascularisation of the iris (NVI), anterior chamber angle (NVA), and retina are common complications of both CRVO and BRVO, although NVI and NVA occur more commonly in CRVO. Neovascularisation can lead to retinal leakage, which might result in macular oedema and severe visual loss (Kooragayala, 2012). Several anti-VEGF therapies have shown promising results in treating CRVO macular oedema in comparison to other therapies (Mitra and Lip, 2011).

DME is an advanced complication of diabetic retinopathy, the most common microvascular complication of diabetes, and accounts for much of the vision loss associated with diabetic retinopathy. The chronic microvascular damage in this condition leads to increased intraocular secretion of VEGF. Aflibercept and other anti-VEGF therapies have demonstrated improvement in visual acuity in patients with DME and have largely replaced laser photocoagulation as the preferred treatment (Boyer, 2013).

As part of the risk management plan for aflibercept, BHC has developed materials to educate both physicians and patients on the key safety information and safe use for aflibercept. BHC has collaborated with RTI Health Solutions (RTI-HS) to develop an observational postauthorisation safety study. The purpose of this study will be to assess physician and patient knowledge and understanding of the key safety information in the aflibercept educational materials developed by BHC. Key content of the materials for physicians includes the importance of using the correct sterile injection technique and monitoring for, and managing, potential injection-related adverse events (AEs). Key content for patients includes steps for preparing for treatment, monitoring for AEs, and steps to take if they identify AEs.

8 Research Question and Objectives

The primary objective of this study is to measure physician knowledge and understanding of the key information in the prescriber guide and intravitreal injection procedure video and patient knowledge and understanding of the key information contained in the patient booklet “Your guide to EYLEA,” patient information leaflet, and audio CD. (The prescriber guide is provided in Annex 3, and the patient booklet and leaflet are provided in Annex 4.)

Specifically, the following objectives will be addressed:

- Investigate whether physicians and their patients have received the educational materials
- Assess physicians' knowledge and understanding of key safety information contained in the prescriber guide and the intravitreal injection procedure video and assess how physicians use the materials in their daily practice
- Assess patients' knowledge and understanding of the key safety information contained in the patient booklet "Your guide to EYLEA," patient information leaflet, and audio CD and determine if the patients used this information

9 Research Methods

9.1 Study Design

The study will be an observational, cross-sectional study of knowledge, understanding, and self-reported behaviour among a sample of physicians and patients with recent aflibercept experience in a total of up to five European countries.

Physicians will be recruited using a random sample of physicians (ophthalmologists) from a physician panel or list with the aim of obtaining a sample generally representative of physicians who have prescribed and administered aflibercept in the selected countries. An invitation will be sent via e-mail or made by phone to the selected sample of physicians, inviting them to participate and providing a link to a web-based questionnaire. Following consent, physicians will be asked to complete the questionnaire evaluating their knowledge and understanding of key safety information, as well as their receipt and use of the aflibercept educational materials.

Patients who have received at least one injection with aflibercept and are returning for a subsequent visit will be recruited by their physicians and invited to participate in the study. The physicians selected for participation in the patient assessment will not be included in the physician assessment described above. Following consent, patients will complete an interviewer-administered questionnaire with primarily closed-ended questions. The patient questionnaire will assess patients' knowledge and understanding of the key safety information in the aflibercept educational materials.

Data from the questionnaire responses will be analysed to ascertain the level of knowledge, understanding, and reported safe use practices among these physicians and patients, stratified by country and other relevant characteristics (e.g., number of prior injections).

9.2 Setting

This cross-sectional study will be conducted in each of five western European countries (the United Kingdom, Germany, France, Spain, and Italy). Five countries are included to provide some diversity in practice patterns and to observe physician and patient knowledge in different settings. In addition, it is anticipated that the drug utilisation in these countries will be such that there will be a sufficient number of eligible physicians and patients with aflibercept experience to participate in the study.

9.2.1 Physician Assessment

A geographically dispersed and diverse set of physicians prescribing aflibercept in each of the five European countries will be selected to reflect the distribution of physician

specialist (ophthalmologist) who prescribe aflibercept. Physicians will be asked to complete an online questionnaire evaluating their knowledge of key safety information as well as their receipt and use of the educational materials for aflibercept. Data will be analysed using descriptive tables summarising demographics, results, and other available characteristics. Timing and sequence of study initiation in each country will be determined based upon the product launch schedule and timing of ethics approval.

9.2.1.1 Physician Selection and Recruitment

The physician sampling frame will be constructed from either a physician panel or prescriber list (e.g., a list of all ophthalmologists who have either prescribed the drug or who have received the educational materials) depending on the availability and completeness of information from each source. The final frame will be determined with the objective of achieving a generally representative sample of physicians prescribing aflibercept. Characteristics such as geographic location and practice setting (e.g., hospital based versus private practice) will be taken into consideration. If the distribution of physicians in the sampling frame appears consistent with the distribution believed in the targeted population, physicians will be randomly selected from the sample frame. However, if the distributions do not appear consistent with the targeted population, the sampling frame will be stratified by geography or other important characteristics, and specific numbers of physicians within each stratum will be selected in order to recruit a sample that matches the distribution in the target population. In this case, the process of selecting physicians for recruitment within each stratum will be made randomly. The final sampling strategy will be determined once aflibercept is on the market and will be designed to ensure appropriate representation.

9.2.1.2 Physician Inclusion Criteria

This study will be conducted with physicians (ophthalmologists) who prescribe and administer aflibercept in the target countries.

To be eligible for the study, physicians must meet all of the following eligibility criteria:

- Licensed and practicing ophthalmologist
- Prescribed and administered aflibercept to at least one patient in the past 6 months

In addition to the physicians who participate in the physician assessment, we will also administer the same questionnaire to the physicians who participate in the patient assessment. Those data will not be pooled with the physician assessment results, but will be used for comparisons between study groups.

9.2.2 Patient Assessment

Patients receiving aflibercept injections will be identified through a diverse selection of medical practices representing physicians who prescribe and administer aflibercept across the target countries. The medical practices selected for participation in the patient assessment will not be included in the physician assessment described previously; however, they will be asked to complete the physician questionnaire to allow exploratory evaluation of the possible impact of the study on physician knowledge and to evaluate patient responses by level of knowledge of their physician. Patients will be invited to participate by their physician and asked to complete an interviewer-administered questionnaire at the site. Data will be collected by in-person interviews with the interviewer entering data directly into the web-based survey system. Care will be taken to ensure that prescriber educational practices are not influenced as a result of participation in the study. Data will be analysed using descriptive tables summarising demographics, results, and other available characteristics. Timing and sequence of study initiation in each country will be determined based upon the product launch schedule and timing of ethics approval.

9.2.2.1 Patient Selection and Recruitment

Patients will be identified by their physician to participate in the study at physician sites (e.g., outpatient centres in hospitals/clinics or private practice offices). At least 10 sites in each country will be selected from a list of eligible physicians to identify and recruit a sufficient number of eligible patients (up to 15 patients per site). Several factors will be evaluated to ensure a diverse representation of sites, including geographic location and patient mix.

9.2.2.2 Patient Inclusion Criteria

To avoid selecting patients who just have received the educational material at the same visit, only those who had already received at least one aflibercept injection within the last 6 months and are returning for a subsequent visit will be recruited.

To be eligible for the study, the patients must meet all of the following criteria:

- Patient has been administered aflibercept at least once within the last 6 months for any indication and is returning for a subsequent visit.
- Patient is aged 18 years or older.
- Patient is able to understand and sign the consent form and patient questionnaire.
- Patient can understand the native language of the country in which the study is being conducted.
- Patient has not participated in a clinical trial for the treatment of an aflibercept indication (e.g., wAMD, CRVO, or DME) in the past 12 months.

Participating sites will identify all patients receiving aflibercept; however, if the patient volume is large, a smaller sample will be selected using a random selection scheme to avoid bias. The sampling approach will be customised for the site based on patient volume and the duration of the data collection period and will be devised to obtain a representative sample of patients at the site. The patient selection strategy will also be designed to assure a reasonable distribution of aflibercept indications within sites. Patients will complete the questionnaire prior to receiving any new education about aflibercept.

9.3 Variables

9.3.1 Physician Questionnaire

The physician questionnaire will contain closed-ended questions (e.g., multiple choice, true/false), with no free-text response fields, eliciting responses measuring physician knowledge and understanding of the key information in the aflibercept prescriber guide and video. The physician questionnaire will include items in the following content areas:

- Sterile techniques to minimise risk of infection, including periocular and ocular disinfection
- Use of povidone iodine or equivalent
- Techniques for the intravitreal injection
- Key signs and symptoms of intravitreal injection–related AEs (i.e., endophthalmitis, cataract, transient intraocular pressure increase, vitreous detachment, and conjunctival and retinal hemorrhage) and medication error/overdose.

In addition to these concepts, the physician questionnaire will include items to characterise the physicians and their practices (e.g., years in practice, patient volume, indications treated with aflibercept) and to investigate physician receipt and use of the prescriber educational materials.

9.3.2 Patient Questionnaire

The patient questionnaire will contain closed-ended questions (e.g., multiple choice, true/false) eliciting responses measuring patient knowledge and understanding of the key information contained in the aflibercept patient booklet “Your guide to EYLEA,” patient information leaflet, and audio CD. The questionnaire will assess patient knowledge of the following concepts:

- Conditions that patients should tell their doctor about before receiving aflibercept
- Key signs and symptoms of AEs (i.e., endophthalmitis, cataract, temporary increase of pressure inside the eye, vitreous detachment, vitreous floaters, and conjunctival hemorrhage)
- What should patients do if they develop a symptom or a suspected side effect

In addition to these concepts, the patient questionnaire will include items to investigate patient receipt and use of the patient booklet "Your guide to EYLEA," patient information leaflet, and audio CD, as well as patient and treatment characteristics (e.g., age, sex, education, time since first aflibercept treatment, and number of aflibercept injections received).

9.4 Data Sources

The source of information for the study will be self-reported data collected from physicians and patients using standard questionnaires with closed-ended response choices.

Questionnaires for physicians and patients have been developed and tested using best practices for instrument development. The questions have been tailored to the study aims and the information provided in the prescriber guide and video and in the patient booklet "Your guide to EYLEA," patient information leaflet, and audio CD. Other questions will obtain information needed to assess potential differences across subgroups and identify any biases (e.g., demographics, experience prescribing and administering aflibercept).

To thoroughly evaluate the physician and patient questionnaires before fielding the study, the questionnaires were tested through cognitive interviews with physicians and patients in each country. Questionnaires were tested in local languages, to ensure that the introductory material, consent forms, and questionnaire items (question stems and response choices) are culturally appropriate and easily and correctly understood by individuals similar to those who will participate in the studies.

Cognitive pretest interviewing is a well-established qualitative research methodology used to identify problems with questionnaire items and response options (Groves et al., 2009). Specifically, trained interviewers ask pretest interview participants to complete the questionnaires while thinking aloud or describing their thought processes as they answer the questionnaire items. Pretest interviewers use an interview guide that includes probe questions designed to help interviewers understand how each participant interpreted and chose his or her answers for each item in the draft questionnaires. The pretest interviews were designed to help identify problems with questionnaire items including the question stems and response choices and to ensure that participants understand the instructions. The pretest interview data were used to optimise the language used in the questionnaires prior to fielding the patient and physician

assessments. Likewise, the cognitive pretest interviews helped identify cultural or translational issues with the draft questionnaires so that they could be modified to meet the individual needs of each country while maintaining comparability across the study.

The pretest interviews also provided an opportunity to test procedures and introductory materials in an effort to increase participation and thoughtful consideration of the questionnaires by participants during collection of the study data. Particular care was paid to patients' opinion on the preferred mode of questionnaire administration to ease the burden of participation among those with limited eyesight. As a result of the pretesting, it was determined that the patient questionnaire should be administered through an in-person interview.

Cognitive pretesting of the physician questionnaire were conducted with 25 physicians across the five study countries who prescribed and administered aflibercept for wAMD or CRVO. Additionally, cognitive pretesting of the patient questionnaire was conducted with 27 patients across countries who were currently being treated for wAMD or CRVO. Physicians who participated in the cognitive pretesting will be excluded from the physician assessment, and patients who participated in cognitive prestest interview will be excluded from the patient assessment.

9.5 Study Size

9.5.1 Physician Sample Size

The study will target 60 to 100 participating physicians per country, for a total of 300 to 500 physicians overall, to allow reasonable precision around estimates of physicians' knowledge and understanding of the prescriber guide. For example, using the assumption that the total sample of participating physicians can be treated as a simple random sample and that the percentage of correct responses to a true/false question is 85%, then for a sample size of 500, the two-sided 95% confidence interval will be 81.6% to 88.0%. Table 1 shows the exact 95% confidence limits assuming various combinations of sample size and correct response percentages.

Table 1. Exact 95% Confidence Limits for Various Combinations of Physician Sample Size and Correct Response Percentage

Physician Sample Size	Correct Response (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
100	80	70.8	87.3
100	85	76.5	91.4
300	80	75.0	84.4
300	85	80.4	88.8
500	80	76.2	83.4
500	85	81.6	88.0

9.5.2 Patient Sample Size

The study will target approximately 150 patients per country, for a total of up to 750 patients overall, to allow reasonable precision around estimates of patients' knowledge and understanding of the key information contained in the patient booklet "Your guide to EYLEA," patient information leaflet, and audio CD. Because we plan to recruit up to 15 patients per physician practice, the responses from patients within the same practice may be correlated. Assuming no intraclass correlation and that the percentage of correct responses to a true/false question is 50.0%, then for a sample size of 750, the two-sided 95% confidence interval will be 46.4% to 53.6%; whereas the corresponding confidence interval will be 42.8% to 57.2% if there is an intraclass correlation of 0.33. Table 2 shows 95% confidence limits assuming various combinations of sample size, correct response percentages, and intraclass correlation coefficients.

Table 2. Confidence Limits (95%) for Various Combinations of Patient Sample Size, Correct Response Percentage, and Intraclass Correlation Coefficient

Patient Sample Size	Intraclass Correlation Coefficient[a]	Correct Response (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
150	0.00	50	42.0	58.0
150	0.11	50	38.7	61.3
150	0.33	50	34.0	66.0
150	0.00	80	73.6	86.4
150	0.11	80	70.9	89.1
150	0.33	80	67.2	92.8
500	0.00	50	45.6	54.4
500	0.11	50	43.8	56.2
500	0.33	50	41.2	58.8
500	0.00	80	76.5	83.5
500	0.11	80	75.0	85.0
500	0.33	80	73.0	87.0
750	0.00	50	46.4	53.6
750	0.11	50	44.9	55.1
750	0.33	50	42.8	57.2
750	0.00	80	77.1	82.9
750	0.11	80	76.0	84.0
750	0.33	80	74.3	85.7

Note: Table calculations assume that, on average, 10 patients come from each practice (cluster).

[a] With an average cluster size of 10 patients, correlation coefficients of 0.11 and 0.33 correspond with a design effect of 2 and 4, respectively.

9.6 Data Collection and Management

9.6.1 Data Collection

9.6.1.1 Physician Data Collection

A web-based electronic data capture (EDC) system will be used in this study. An invitation will be sent via e-mail or made by phone to the selected sample of physicians, inviting them to participate and providing a link to the web-based questionnaire. During the data collection period, invitations will be sent to each sampled physician up to three times. Each invited physician will be asked to log in to the study website by entering a unique identification number and password assigned to each participant and provided in the invitation to participate. The questionnaire will begin with informed consent. After participants consent, they will be prompted to complete the questionnaire. A screening question will be included at the beginning of the questionnaire to confirm that the physician has administered aflibercept at least once within the past 6 months.

The questionnaire will be self-administered (closed-ended questions with predefined answers) and can be completed at the participants' convenience. Although participants will be encouraged to complete the questionnaire in a timely manner, once they start the questionnaire, they will be able to stop at any point and, at a later time, pick up where they left off, should that be necessary. Participants will not be able to go back and change answers to previous questions. This restriction minimises the likelihood of the respondent searching for answers via the web or other sources or being influenced by answers to subsequent questions.

Participants will also not be allowed to regain access to the questionnaire once it has been completed. Based on potential country-specific requirements, the recruitment process and physician questionnaire may be different between countries. Country-specific differences will be described and appended to the final study protocol.

9.6.1.2 Patient Data Collection

The patient questionnaire will be administered in person by a trained interviewer to facilitate participation by patients with limited visual acuity. Patients will be invited to participate by their physician.

Sites will keep a simple register with information on the number of patients approached about the study, the number of patients confirmed eligible, and the number of patients who refused. These data will allow calculation of the participation rate. Patients who are approached by the study coordinator and then refuse to participate will be asked the reason for refusal. Reasons for non-participation will be described in the report. Participating sites will also be asked to collect a limited amount of de-identified information on all patients receiving aflibercept (e.g., age range, sex, indication) so that characteristics of participants can be compared with those of non-participants.

Informed consent will be obtained from each eligible and interested patient prior to completion of this questionnaire. If the patient is unable to read the consent form on his or her own (e.g., because of poor vision), another adult (e.g., a caregiver, family member, friend) may read the consent to the patient, and the patient will sign the consent. The interviewer will administer the questionnaire to the patient in a private setting in the physician's office and will be trained in such a way as to minimize influence by the site in this process. While participating physicians will be informed of the purpose of the study, they will be counselled not to alter routine practice and patient education so as not to influence the study results. Physicians will be advised that the ultimate goal of the study is to evaluate the educational materials.

9.6.2 Data Management

A data management plan will be developed to guide the handling of data, including the transfer of electronic files. The data management plan will include, if necessary, country-specific modifications due to local regulations or requirements. For the physician assessment, physicians will enter data directly into a web-based EDC system. For the patient assessment, the site interviewers will record patient responses to the questionnaire on a paper form and then enter the data into the EDC system. Edit and logic checks will be embedded in the EDC system, and queries will be presented to the data entry person to ensure high-quality data. However, due to the self-reported nature of the data, some such queries may not be possible to resolve.

RTI-HS data managers will conduct user acceptance testing of the EDC system and will sign the user acceptance testing report before the EDC system is used in the field. Staff will be trained on data collection forms and the EDC system before the study is fielded. RTI-HS data managers will approve the data management plan, all annotated data collection forms, the EDC system, the data cleaning specifications document, and the testing summary reports before authorising the data systems to go "live." RTI-HS data managers will ensure that the EDC system is tested and valid, and will require that testing documentation, database documentation, and change control documentation will be created and maintained.

Once the system is in the field, data management activities will include review of interim analysis files for consistency, programming edit checks in preparation for statistical analysis, and merging datasets if required.

9.6.2.1 Record Retention

Following completion of the patient assessment, registers will be stored for 15 years. Enrolment logs, informed consent forms, and hardcopy patient questionnaires will remain at the sites. All data for the physician assessment will be electronic. Any paper forms collected in the European Union will be maintained within the European Union. Only de-identified data based on case identification numbers will be transferred to the United States (US) for the purpose of analysis and generation of the final report. De-

identified electronic data sets will be stored in the US for 15 years from the time of final results submission.

9.7 Data Analysis

Analyses will include detailed review of responses to individual questions and potential summary measures across logical grouping of response items. A detailed analysis plan describing methods of analysis and presentation and including table shells will be developed prior to starting analysis of data.

Descriptive tables summarising demographics, questionnaire response results, and other available characteristics will be generated for the physicians and patients, stratified by country and other variables of interest. For continuous-type data, the mean, standard deviation, median, and range will be presented. For categorical data, frequencies and percents will be reported. The specific tables to be included will be finalised in the analysis plan. Weighting of results will be considered, as appropriate based on sampling stratification.

The analysis will include a comparison of participants to non-participants, if data are available. We will also compare characteristics of the participants to what is known about the overall physician and patient populations, if data are available. In addition, exploratory analyses will be conducted comparing responses between the physicians who participated in only the physician questionnaire component of the study to those who also participated in recruiting patients for the patient component to explore the potential that the study itself created greater awareness of the safety information. Multivariable analyses may be conducted to evaluate predictors of high/low knowledge levels.

Typically, questionnaire data are mostly complete, and each question will be analysed individually among those participants who respond. However, as part of the analysis plan, we will establish a threshold of data required for a questionnaire to be included in the analysis. If substantial data are missing on key variables, we will consider removing the participant from the analysis.

The analysis plan will also describe the following:

- Analysis of subgroups, including stratification variables
- Methods for handling missing data
- Level of statistical precision

All analyses will be performed using SAS 9.2 (or higher) statistical software (SAS, Cary, North Carolina). Programmes, logs, and output will be reviewed for accuracy according to relevant standard operating procedures.

9.8 Quality Control

This project will be conducted in accordance with the guidances described in Section 10.2 (Ethical, Regulatory, and Scientific Principles) and the internal standard operating procedures of participating institutions. The RTI-HS Office of Quality Assurance, an independent unit that reports to the Vice President of RTI-HS, will oversee quality assurance for this study.

Standard operating procedures will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

All programming written by one study analyst will be independently reviewed by a different analyst, with oversight by a senior statistician. All key study documents, such as the analysis plan, data collection forms, and study reports, will undergo quality-control review, senior scientific review, and editorial review.

For RTI-HS, OQA will perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation, data entry and data transfer procedures and documentation, and institutional review board (IRB) documentation. Such audits will be conducted by the OQA according to established criteria in standard operating procedures and other applicable procedures.

9.9 Strengths and Limitations of the Research Methods

A key strength of the study is the planned diversity of the sites, physicians, and patient populations to be included in both assessments. Based on available information, geographic location, and practice type (e.g., clinic/hospital, physician office), sites and patients recruited for participation should constitute a generally representative sample of aflibercept prescribers and users. However, depending on the timing of product availability relative to the timing of data collection, it might be challenging to ensure that the finally selected centres, prescribers, and patients are fully representative of actual prescribers and patients across countries and different types of centres.

The physician assessment will be conducted after physicians have received the prescriber guide and have had a chance to utilise that guide in their practice. This portion of the study will evaluate how well they understand the safety information provided in the educational materials and apply it to their practices.

The patient assessment will be conducted after patients have received at least one administration of aflibercept and have had the opportunity to receive the educational materials for patients. Therefore, the study will evaluate recall about the process of

receiving and reviewing the patient booklet "Your guide to EYLEA," patient information leaflet, and audio CD and awareness of the key information contained in these resources.

Among the strengths of the patient assessment will be the collection of information on participants and on non-participants. Sites will keep a simple register with information on the number of patients approached about the study, the number of patients confirmed eligible, and the number of patients who refused. These data will allow calculation of the participation rate. Patients who are approached by the study coordinator and then refuse to participate will be asked the reason for refusal. Reasons for non-participation will be described in the report. In addition, characteristics of the participants will be compared with those of the general population of aflibercept patients (to the extent information is available) to evaluate any differences that should be considered in the analysis.

Other strengths of the patient assessment include the probability of high response rates given that the study is being introduced to patients by a trusted physician, and the ability to stratify knowledge results based on based on duration of use of aflibercept; patient use and receipt of the patient booklet "Your guide to EYLEA," patient information leaflet, and audio CD; and provider knowledge. Furthermore, physicians who are recruited for the patient assessment will be asked to complete the physician questionnaire to explore the potential that the study itself created greater awareness of the safety information.

The study will target a total of 300 to 500 physicians (60 to 100 physicians per country) and 750 patients (approximately 150 patients per country) to complete the assessment. The majority of the analysis will focus on aggregated data. Although the report may display country-specific and indication-specific findings, there may be limitations with drawing country- or indication-specific conclusions, particularly for the patient assessment given the relatively small samples sizes within each country and indication.

As with all voluntary studies, some limitations are inherent. Although the study is designed to ensure the selection of a diverse and generally representative sample of prescribers and patients to participate in this study, there exists no exhaustive list of all aflibercept prescribers and patients from which to draw a sample; hence, it is impossible to select a random sample of all prescribers/patients. Therefore, the study participants may not necessarily represent all users of aflibercept. In addition, as is true with most surveys, it is possible that respondents who complete the questionnaire will differ from non-respondents in characteristics measured in the questionnaire (e.g., knowledge, reading the educational materials). The direction and magnitude of such potential respondent bias is not known. In addition, the sample does not account for individuals who could not participate because of the mode of data collection (i.e., Internet access). However, it is anticipated that the majority of physicians will have Internet access. A comparison of participants and non-participants in the physician assessment may not be possible because physicians who do not wish to participate in the survey are likely not to

respond to the invitation. However, if data are available, we will compare characteristics of the participants to what is known about the overall physician populations.

Another potential limitation of the patient assessment is that the study could influence sites to provide more education to patients than they normally would provide. To minimise this risk, sites will be trained to provide only limited information about the study prior to the patients' participation in the study, and patients will be asked to complete the questionnaire at the site prior to receiving any additional counseling about treatment.

10 Protection of Human Subjects and Other Good Research Practice

10.1 Protection of Human Subjects

This study will be conducted in accordance with all applicable ethical and regulatory requirements, including, where applicable, the 1996 version of the Declaration of Helsinki. The IRB at RTI International (of which RTI-HS is a division) will review the study protocol, questionnaires, and informed consent documents. IRB/ethics committee (EC) approvals will be obtained in accordance with applicable national and local regulations in each country.

10.2 Ethical, Regulatory, and Scientific Principles

This study is being conducted as a regulatory commitment. As an observational study, the risks for patients linked to their participation in the study are limited to a breach of confidentiality with regard to personal identifiers or health information. Before a patient can participate in the study, he or she must give informed consent. Independent EC approval will be according to the guidance of the each country's research ethics requirements.

The study will be conducted under the following guidelines:

- The study is a postauthorisation safety study (PASS) and will comply with the definition of the non-interventional (observational) study referred to in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use tripartite guideline *Pharmacovigilance Planning E2E* (ICH, 2004) and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies* (rev 1), (EMA, 2013), and with the 2012 European Union pharmacovigilance legislation, adopted June 19, 2012 (European Commission, 2012). The study will comply with the study reporting requirements specified in Module VIII section VIII.B.6.3.1. "Progress reports" and VIII.B.6.3.2. "Final study Report" of the *Guideline of Good Pharmacovigilance Practices* (EMA, 2013).

- The study will be registered in the European Network of Centres of Pharmacoepidemiology and Pharmacovigilance (ENCePP) EU PAS Register (ENCePP, 28 July 2014).
- This study adheres to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)* (International Society for Pharmacoepidemiology, 2007).
- The study has been designed in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology, revision 3* (ENCePP, 2014).
- The study will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (STROBE, 2007).

10.3 Informed Consent

Participant informed consent will be obtained for each patient or physician who agrees to complete a questionnaire. Patient informed consent will be obtained in writing in all participating countries. If the patient is unable to read the consent form on his or her own, another adult may read the consent to the patient, and the patient will sign the consent. Physicians will be asked to provide electronic acknowledgement of consent prior to completing the Web-based questionnaire.

10.4 Participant Confidentiality

For the patient assessment, sites will maintain a patient ID log with the names and study identification numbers of patients approached about the study. Patient ID logs will be maintained at the site and will not be shared with the research team, third parties, or BHC. Additionally, the patient questionnaire will *not* be linked to the patient's name or any other patient-identifying information. Finally, age range in lieu of a birth date will be used to further protect confidentiality.

For the physician assessment, physicians will be given unique login information to complete the survey. The personal identifying information collected from physicians will be limited to that which is necessary for compensation purposes and to meet regulatory requirements for reporting payments made to physicians in each country, as applicable.

Only de-identified data will be made available to BHC. Thus, any reports generated will not contain any participant identifiers. Data will be provided to BHC in aggregate only and will not be linked to individual patients or physicians.

10.5 Compensation

Physician sites participating in the patient assessment will be paid nominal incentives to compensate them for the time spent recruiting patients and providing limited data from

patient records, per country-specific regulations. The amount and payment methods will be reviewed and approved by the EC to ensure that payments are commensurate with the time needed to complete the study tasks and are not coercive.

Physicians participating in the physician assessment will also be paid nominal incentives to compensate them for their time in completing the study questionnaire.

11 Management and Reporting of Adverse Events/Adverse Reactions

This study is not designed to collect information on individual adverse drug events, which are better collected using other study designs. However, spontaneous AEs may be identified through the following pathways:

- Communicated by patients or physicians during the qualitative cognitive pretesting interviews
- Communicated by the patient to the site interviewer during completion of the interviewer administered questionnaire

For both the cognitive pretest interviews and interviewer-administered patient questionnaires, the interviewer will undergo safety training and will complete an AE report form if an AE is reported. The case report form will be submitted to the BHC pharmacovigilance country head (PVCH) within 1 business day. Adverse event reports for both Bayer and non-Bayer products will be collected and reported to BHC. Adverse events related to a non-Bayer product will be reported by BHC to the pharmacovigilance department of the marketing authorisation holder of the non-Bayer product within the frame of local laws and regulations as well as the respective pharmaceutical company's reporting system. For AEs related to Bayer products, BHC will assess the information for possible AEs and product complaints and forward it for processing to the company safety database and/or to the Product Complaints group as applicable through BHC's usual reporting processes and standard operating procedures. The local contact to the PVCH will follow up with the patient's physician if BHC determines that follow-up is needed and if the reporting patient has given consent for their physician to be contacted by BHC. All initial and follow-up information will be de-identified.

Any AE information received will be documented and reported following the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VI – Management and Reporting of Adverse Reactions to Medicinal Products* (EMA, 2012) and in accordance with EMA regulations (Regulation 520/2012 on the performance of pharmacovigilance activities provided for in Regulation [EC] No 726/2004). The process for safety reporting will be further described in a safety reporting plan.

12 Plans for Disseminating and Communicating Study Results

The protocol, study status updates, and report(s) will be included in regulatory communications in line with the risk minimisation plan, periodic safety update reports, and other regulatory milestones and requirements.

In the case of communications in other settings (such as conferences or publications), abstracts, presentations, and manuscripts will be prepared in accordance with the guidelines of the International Society for Pharmacoepidemiology (2007) and the International Committee of Medical Journal Editors (2010).

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Annex 1.
List of Stand-Alone Documents

None.

Annex 2. ENCePP Checklist for Study Protocols

Doc.Ref. EMEA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is “Yes”, the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer ‘N/A’ (Not Applicable) can be checked and the “Comments” field included for each section should be used to explain why. The “Comments” field can also be used to elaborate on a “No” answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good Pharmacovigilance Practices (GVP).

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	12
1.1.2 End of data collection[2]	☒	☐	☐	12
1.1.3 Study progress report(s)	☒	☐	☐	12
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	12
1.1.6 Final report of study results	☒	☐	☐	12

Comments:

1.1.4 - Due to the relatively short data-collection period, the study will include only a final report.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	13-14
2.1.2 The objectives of the study?	☒	☐	☐	14-15
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	17-18
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 if applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Comments:

2.1.5 - The study is descriptive. There are no a priori hypotheses.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	16
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	19-20
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	25

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	17-18
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	17-18
4.2.2 Age and sex?	☒	☐	☐	18
4.2.3 Country of origin?	☒	☐	☐	16
4.2.4 Disease/indication?	☒	☐	☐	18
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	17-18

Comments:

4.2.2 – There are no specified inclusion/exclusion criteria for sex; all will be included. Only patients aged 18 years or older will be included; there are no age limits on physician participation.

4.2.5 and 4.2.6 – Comorbidities and seasonality have not been identified as relevant to the analysis of study results.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☒	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

This is a study of physician and patient knowledge of safety and safe use information for aflibercept. It is not a study of exposure to a medication and clinical outcomes.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	19-20
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

This is a study of physician and patient knowledge of safety and safe use information for aflibercept. It is not a study of exposure to a medication and clinical outcomes.

Outcomes in this study include self-reported responses to questions on knowledge and behaviour. The study materials were evaluated in each group (physicians and patients), in each country, through cognitive pretesting.

There is no validation of self-reported information.

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☒	☐	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	

Comments:

This is a study of physician and patient knowledge of safety and safe use information for aflibercept. It is not a study of exposure to a medication and clinical outcomes.

The study will capture information on participant characteristics that may be related to the study outcomes (prevalence of accurate knowledge), such as age, experience with the product, and having received and read the educational information.

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	18 and 23
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	20
8.1.3 Covariates?	☒	☐	☐	20
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	20
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	20
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	20
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

8.3 – There will be no need for coding of responses in these studies. Analyses will evaluate the responses to the questionnaire items.

8.4 – This study does not involve linkages between data sources.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	21-22

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	25
10.3 Are descriptive analyses included?	☒	☐	☐	25
10.4 Are stratified analyses included?	☒	☐	☐	
10.5 Does the plan describe the methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

This is a study of physician and patient knowledge of safety and safe use information for aflibercept. It is not a study of exposure to a medication and clinical outcomes. Analyses described in the protocol are primarily descriptive, summarizing the responses to individual questionnaire items. A statistical analysis plan will be developed with details of analysis stratification, any weighting of results, and possible multivariable analyses of predictors of high/low knowledge levels.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	25
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	24-25
11.3 Are methods of quality assurance described?	☒	☐	☐	26
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	26-28
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

11.5 – Investigators performing the study will review and interpret the data prior to sharing the initial draft report with the sponsor.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	19 26-28
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	26-28

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	20-21
12.3 Does the protocol address other limitations?	☒	☐	☐	26-28

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/ Institutional Review Board approval been described?	☒	☐	☐	28
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	29

Comments:

13.2 - Institutional Review Board/Ethics Committee approvals will be obtained in accordance with applicable national and local regulations in each country prior to data collection.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	12

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	31
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	31

Comments:

Elizabeth Andrews, PhD, MPH

Name of the main author of the protocol: Laurie Zografos, BS

Date: / /

Signature: _____

Annex 3. Prescriber Guide

** This document represents content only and not layout **

Recommendations for treatment with

Prescriber Guide

Content ..... Page

GENERAL INFORMATION

Before the start of treatment with EYLEA, a patient information booklet, including an audio CD and the Patient Information Leaflet, must be provided to each patient who is prescribed EYLEA.
The physician is responsible for providing the patient with these materials. In addition, the implications of anti-VEGF treatment should be explained.
Specifically, any signs and symptoms of serious adverse events and when to seek medical attention should be discussed with the patient.

Therapeutic indications

EYLEA is indicated for adults for the treatment of:

- **neovascular (wet) age-related macular degeneration (AMD)**
- **visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)**
- **visual impairment due to diabetic macular oedema (DME)**

Product information

- **EYLEA 40 mg/ml solution for injection**
- **EYLEA is for intravitreal injection only. It must only be administered by a qualified physician experienced in administering intravitreal injections**
- **The solution is a clear, colourless to pale yellow, and iso-osmotic solution**
- **The solution should be inspected visually for any foreign particulate matter and/or discolouration or any variation in physical appearance prior to administration. In the event of either being observed, discard the medicinal product**
- **The pre-filled syringe and the vial are for single use only**

Qualitative and quantitative composition

- **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. 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**
- **One vial contains an extractable volume of 100 microlitres, equivalent to 4 mg aflibercept. This provides a usable amount to deliver a single dose of 50 microlitres containing 2 mg aflibercept. 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**

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**
- **Keep the vial in the outer carton in order to protect from light**
- **Prior to usage, the unopened vial or blister of EYLEA may be kept at room temperature (below 25°C) for up to 24 hours. Do not open the sterile, pre-filled blister outside the clean administration room. After opening the blister or vial, proceed under aseptic conditions**

Dosing recommendations

- **The recommended dose for EYLEA is 2 mg aflibercept, equivalent to 50 microlitres**
- **Please note that the dosing recommendations for wAMD, CRVO, BRVO and DME are different to each other and are as described below:**

wet AMD

- **EYLEA treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections**
- **After the first 12 months of treatment with EYLEA, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections**

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

- After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month.
- If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, Eylea should be discontinued.
- Monthly treatment continues until maximum visual acuity 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 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. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly.
- The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response.
- Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography).

Diabetic Macular Oedema

- **EYLEA treatment is initiated with one injection per month for five 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. The schedule for monitoring should be determined by the treating physician.**
- If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, EYLEA should be discontinued.

Contraindications

- **Hypersensitivity to aflibercept or to any of the excipients listed in section 6.1 in the SmPC**

- **Active or suspected ocular or periocular infection**
- **Active severe intraocular inflammation**

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Intravitreal injection-related reactions

Intravitreal injections, including those with Eylea, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Proper aseptic injection techniques must always be used when administering Eylea. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay.

Increase in intraocular pressure

Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with EYLEA. Special precaution is needed in patients with poorly controlled glaucoma (do not inject EYLEA while the intraocular pressure is ≥30 mm Hg). In all cases, both intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed according to clinical practice.

Immunogenicity

As this is a therapeutic protein, there is a potential for immunogenicity with EYLEA. Patients should be instructed to report any signs or symptoms of intraocular inflammation, (eg, 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, CRVO, BRVO and DME other considerations apply including:

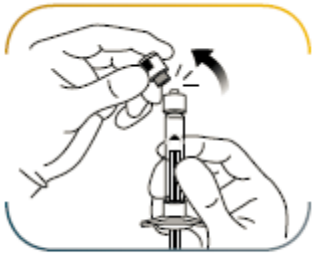
- **Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept**

INSTRUCTIONS FOR USE / HANDLING

Injection preparation:

- **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 (eg, 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 sterilised eyelid speculum (or equivalent) are recommended**
- **For the intravitreal injection, a 30 G x ½ inch injection needle should be used**

Pre-filled syringe:



Please note: Snap off (do not turn or twist) the syringe cap.

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.**

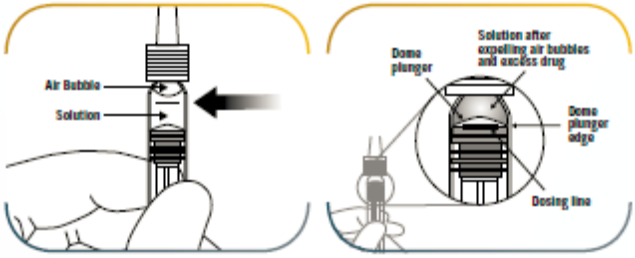
3 **To remove the syringe cap, hold the syringe in one hand while using the other hand to grasp the syringe cap with the thumb and forefinger.**

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). The excess volume needs to be expelled before injecting EYLEA to avoid overdose.**

9 **The pre-filled syringe is for single use only. Any unused medicinal product or waste material**

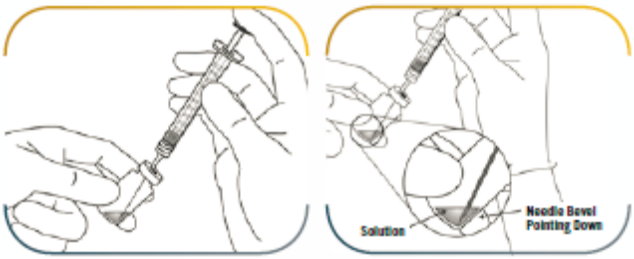
should be disposed of in accordance with local requirements.

Vial:

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

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

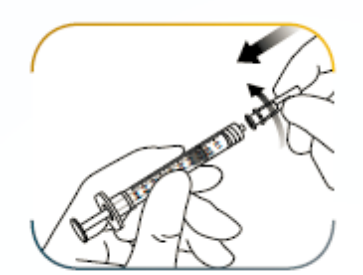
3 Push the filter needle into the centre of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.



4 Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid.

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

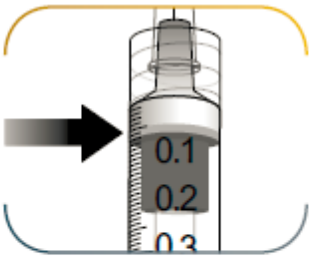
6 Remove the filter needle and properly dispose of it. Note: filter needle is not to be used for intravitreal injection.

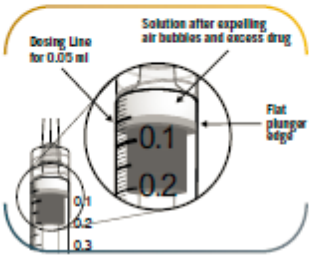


7 Using aseptic technique, firmly twist a 30 G x ½ - inch injection needle to the Luer-lock syringe tip.

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. The excess volume needs to be expelled before injecting EYLEA to avoid overdose.

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

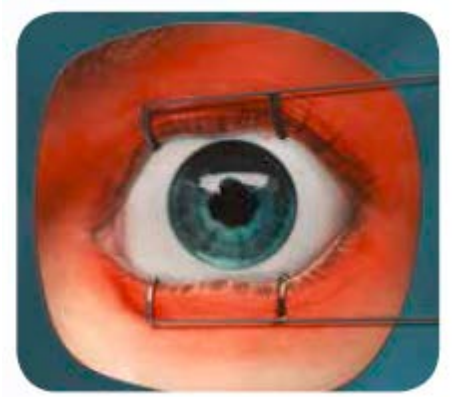
INJECTION PROCEDURE

For use of topical antibiotics please refer to local or national clinical guidelines.

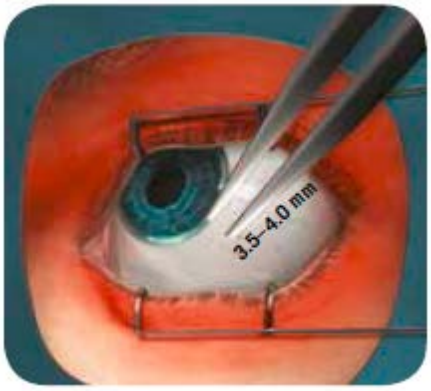
1. Administer topical anaesthesia.

2.Instill disinfectant (eg, 5% povidone iodine solution or equivalent) applied to eyelids, eyelid margins and into the conjunctival sac.

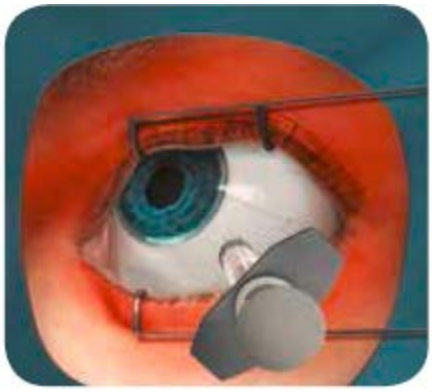
3. A disinfectant (eg, 10% povidone iodine solution or equivalent) may also be applied to the periocular skin, eyelids, and eyelashes, avoiding extensive pressure to eye glands.



4. Cover with sterile drape and insert sterile lid speculum.



5. **Tell your patient to look away from the injection site. Position the eye adequately. At an area 3.5 to 4.0 mm posterior to the limbus, mark an injection site.**



6. **Insert the injection needle 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.**

Other sources of information include

- Intravitreal guidelines and techniques ONE® Network. The ophthalmic news and education network. American Academy of Ophthalmology. http://one.aao.org/focalpointssnippetdetail.aspx?id=f759cd36-2047-4608-a78c-9bbd42fa7cac. Accessed 26 January 2015.
- Guidelines for Intravitreal Injections Procedure 2009. The Royal College of Ophthalmologists. Available at: http://www.rcophth.ac.uk/page.asp?section=451. Accessed 26 January 2015.
- Age-Related Macular Degeneration: Guidelines for Management, September 2013. Available at: http://www.rcophth.ac.uk/page.asp?section=451. Accessed 26 January 2015
- Jaissle GB et al. Recommendation for the implementation of intravitreal injections--statement of the German Retina Society, the German Society of Ophthalmology (DOG) and the German Professional Association of Ophthalmologists (BVA). Klin Monbl Augenheilkd. 2005 May;222(5):390-5. *Article in German*
- Société Fançaise d'Ophtalmologie. Guidelines for intravitreal injections. http://www.feoph-sight.eu/?p=211. Accessed 26 January 2015. *In French or English*
- Intravitreal Injection Procedure Video

AFTER THE INJECTION

- Evaluate vision immediately after injection (hand movement or finger counting)
- 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 (eg, eye pain, redness of the eye, photophobia, blurring of vision) without delay
- Application of antibiotic eye drops after intravitreal injections should be according to local ophthalmologic society guidelines.

ADVERSE DRUG REACTIONS

See section 4.8 of the Summary of Product Characteristics for full list of undesirable effects

- Endophthalmitis
  Patients may experience eye pain or increased discomfort, worsening eye redness, photophobia or sensitivity to light, swelling, and vision changes, such as a sudden decrease in vision or blurring of vision.
- Transient increased intraocular pressure
  Patients may experience halos around lights, red eye, nausea and vomiting, and vision changes.
- Cataract (traumatic, nuclear, subcapsular, cortical) or lenticular opacities
  Patients may experience less vivid lines and shapes, shadows, and colour vision than before, and vision changes.
- Tear or detachment of the retinal pigment epithelium
  Patients may experience sudden flashes of light, a sudden appearance or an increase of the number of vitreous floaters, a curtain over a portion of their visual field, and vision changes.

Management of injection related adverse events:

In any case of an adverse event that concerns your patient, your patient must have immediate access to an ophthalmologist.

Appropriate management of ALL adverse events, including those associated with the intravitreal injection, should be carried out according to clinical practice and / or following standardised guidelines.

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare Professionals are asked to report any suspected adverse reactions. See section 4.8 of the Summary of Product Characteristics for how to report adverse events.

APPROPRIATE LOCAL SAFETY INFORMATION

Insert appropriate local safety information

For more information about EYLEA®, visit www.eylea.com

Bayer Pharma AG, D-13342 Berlin,
Germany
www.bayerhealthcare.com

Annex 4. Patient Booklet, “Your Guide to EYLEA”

NB **

1. **This document represents content only and is NOT in final layout form. Final layout form is the decision of the local country.**

2. **Patient brochures maybe combined or used individually per indication. Use per individual indication is recommended.**

3. **Sections identical to each indication brochure are grouped at the end.**

Your guide to EYLEA®

The brochure has been produced for people who have been prescribed EYLEA (aflibercept solution for injection)

EYLEA is used to treat Diabetic Macular Oedema (DME)

Welcome to your EYLEA guide

Your doctor has prescribed EYLEA because you have been diagnosed with diabetic macular oedema, or DME. This is a condition that is making it harder for you to see clearly. Treatments like EYLEA can help stop your eyesight from becoming worse, and may improve some of the symptoms you have.

This booklet also contains an audio CD with all of the information contained in this book.

Whether you read this guide or choose to listen to it on CD, it has been made to help answer any questions you may have, so you can get the most out of your treatment.

Your eye care clinic is:

Contact:

Telephone:

Address:

Email:

Within this book you will find:

- Information to help you understand DME
    - What is DME?
    - What causes DME?
    - Advice for living with DME

- What to expect from your EYLEA® treatment
    - What is EYLEA?
    - How will I take EYLEA?
    - What if I have questions about EYLEA?

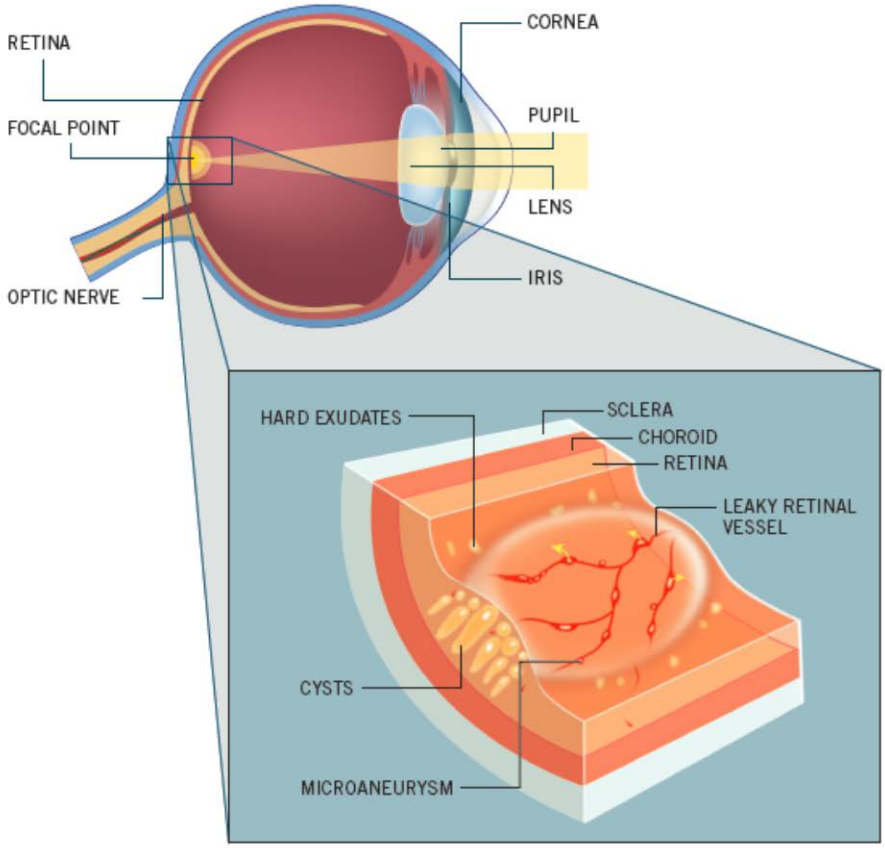
- How to care for your eyes after your EYLEA treatment
    - What should I expect?
    - When do I need to take EYLEA again?
    - Are there side effects with EYLEA?

There is also useful information about support groups for DME and a calendar to help you keep track of your EYLEA treatment.

What is DME?

Within the back of your eye, there is a network of tightly woven cells and blood vessels that form a barrier to control substances entering or leaving your retina. The retina is where all of the images you see are recorded – it acts like the film in a camera.

People with DME have a damaged barrier that allows fluids to leak through. This leakage causes swelling. The macula is the part of the retina responsible for central and fine vision. When the macula swells with fluid, central vision becomes blurry. Over time the swelling can create scars which damage the retina. Like scratches on a photograph, these scars make it harder for you to see all that you should.



What causes DME?

DME is caused by long-term exposure to high blood sugar levels, known as hyperglycaemia. This is generally caused by diabetes that either wasn't diagnosed early or hasn't been consistently controlled.

Other things that can increase your risk of worsening DME, are 'lifestyle' factors including smoking and being overweight. Quitting smoking greatly lowers the risk of damage to your eyes as well as improving your general health. If you are overweight, losing weight and eating healthily can help protect your eyesight. Your general practitioner can help you with quitting smoking and losing weight.

The best things you can do to protect your eyesight are to follow your eye doctor's advice and to make sure you keep all of your scheduled appointments.

How is DME treated?

There are several treatment options for DME and they work in different ways. Generally, these treatments work by shrinking and sealing up the leaking blood vessels. These treatments can involve injections or laser surgery.

Since no two people are alike, there is no one-size-fits-all solution. Your doctor will choose a treatment best-suited for your individual needs.

What is EYLEA?

EYLEA is a type of treatment known as an anti-VEGF. This is an abbreviation for anti-vascular endothelial growth factor, which is a description of how EYLEA works to protect your vision. EYLEA blocks a particular protein that creates leaky blood vessels. This helps reduce the swelling in the retina and protects your vision.

EYLEA is a solution (a liquid) that is injected into the eye. While it is understandable to worry about an injection, most people who have EYLEA treatment say that the injection is painless and it sounds worse than it really is.

Who is EYLEA for?

EYLEA is for people who have been diagnosed with DME.

Before your EYLEA treatment starts, make sure to tell your doctor or nurse if you:

- Have an infection in or around your eye
- If you currently have redness in your eye or if there is any pain in your eye
- Think you may be allergic to iodine, any pain killers or any of the ingredients in EYLEA
- Have had any issues or problems with eye injections before
- Have glaucoma or a history of high pressure in your eye
- If you see, or have seen, flashes of light or ‘floaters’ in your vision
- Are taking any medications, with or without a prescription
- Are pregnant, planning to become pregnant or breastfeeding. There is no experience of using EYLEA in pregnant women. EYLEA should not be used during pregnancy, discuss this with your doctor before treatment with EYLEA. Women of child bearing potential should use effective contraception during their treatment and for at least three months after the last injection of EYLEA
- Had or will have eye surgery within four weeks before or after EYLEA treatment

How can I get ready for my EYLEA appointment?

Your doctor may ask you to take eye-drops for a few days before your appointment. After your treatment, your vision may be blurry so you should not drive home. Plan to have a friend or family member take you to your appointment or arrange another way to get there and home again. On the day of your appointment, do not wear any makeup.

What can I expect at my EYLEA appointment?

Your doctor or nurse will get you ready for your EYLEA treatment. These people are highly trained professionals with experience in treating DME. They understand that the treatment procedure may sound concerning and they will take extra care to make sure you are relaxed and comfortable.

You will be given eye drops which act as a local pain killer and an eyewash will be used to clean your eye and the skin around it. Your face will be covered by a special drape and your eye will be held open. The local pain killer will blur your vision so you will not see the needle.

An experienced doctor will give the injection into the white of your eye. Most people say the injection is painless and some say they feel a slight pressure. The whole procedure may feel a bit uncomfortable, but is over in a few minutes.

For this section refer to common page

For this section refer to common page

For this section refer to common page

Living with DME

Being diagnosed with DME and experiencing problems with your eyesight can be an anxious time. It is normal to worry and feel uncertain about your future, but your diagnosis doesn't mean you can no longer live a full life. You can continue to enjoy family, friends and interests with some small changes.

Some helpful adjustments include:

- Tell friends and family that you have DME and it affects your vision
- Use brighter lighting
- Organise your surroundings so everything has a place
- Carry and use a torch and magnifying lenses when about
- Read large print books and newspapers and try audio books

Support for people with DME

Wherever you are and however much you are affected by DME, it is important to remember that you are not alone. It may be difficult to understand your diagnosis or to come to terms with it. Speaking to experts can help answer questions you may have, and speaking to others who are in, or have been in, a similar situation to yourself can help you come to terms with your diagnosis.
[Links to be added]

For this section refer to common page

Your guide to EYLEA®

The brochure has been produced for people who have been prescribed EYLEA (aflibercept solution for injection)

EYLEA is used to treat Central Retinal Vein Occlusion (CRVO)

Welcome to your EYLEA® guide

Your doctor has prescribed EYLEA because you have been diagnosed with central retinal vein occlusion, or CRVO.

This is a condition that is making it harder for you to see clearly. Treatments like EYLEA can help stop your eyesight from becoming worse, and may improve some of the symptoms you have.

This booklet also contains an audio CD with all of the information contained in this book.

Whether you read this guide or choose to listen to it on CD, it has been made to help answer any questions you may have so you can get the most out of your treatment.

Your eye care clinic is:
Contact:
Telephone:
Address:
Email:

Within this book you will find:

- Information to help you understand CRVO
  - What is CRVO?
  - What causes CRVO?
  - Advice for living with CRVO

- What to expect from your EYLEA® treatment
  - What is EYLEA?
  - How will I take EYLEA?
  - What if I have questions about EYLEA?

- How to care for your eyes after your EYLEA treatment
  - What should I expect?
  - When do I need to take EYLEA again?
  - Are there side effects with EYLEA?

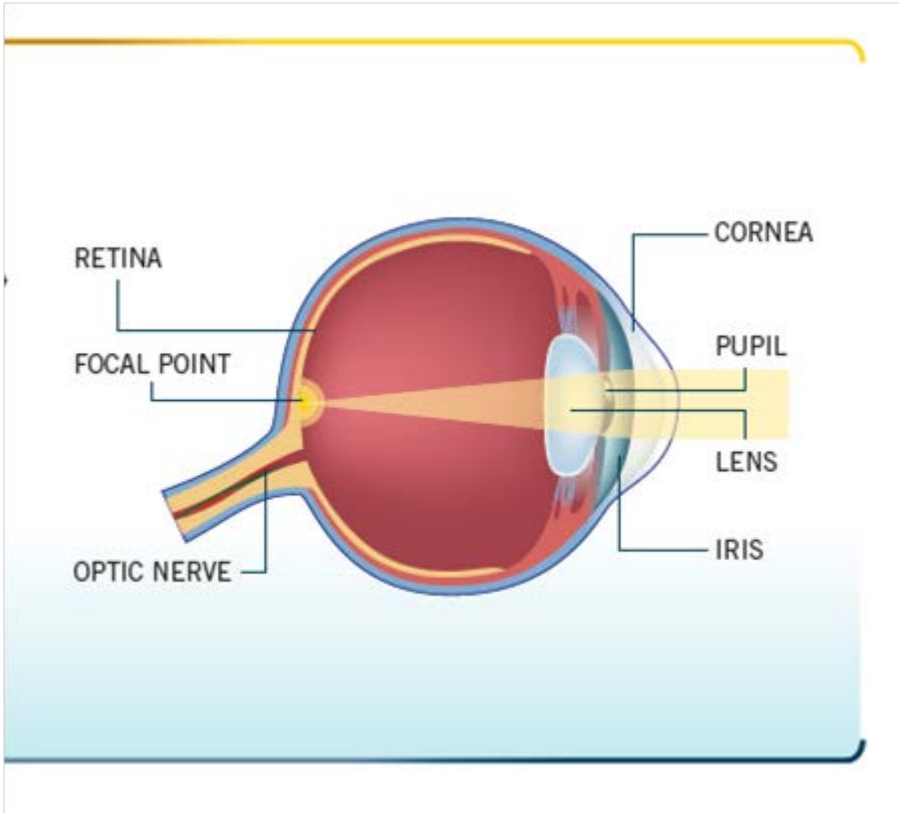
There is also useful information about local support groups for CRVO and appointment reminders to help you keep track of your EYLEA treatment.

What is CRVO?

Central retinal vein occlusion is a condition that damages your eyesight by blocking the flow of blood to and from the retina, in the back of your eye.

The retina is where all of the images you see are recorded – it acts like the film in a camera.

The blockage stops blood from flowing in and out of the retina which can damage your eyesight and eventually lead to blindness and a painful eye.



What causes CRVO?

Central retinal vein occlusion can happen at any age, but is more common in people over 65 years.

In many people with CRVO, a specific cause can't be determined but it often happens as a consequence of other conditions like glaucoma, hypertension (high blood pressure) or diabetes.

Other things that can increase your risk of getting CRVO, or having it get worse, are 'lifestyle' factors including smoking and being overweight. Quitting smoking greatly lowers the risk of damage to your eyes as well as improving your general health. If you are overweight, losing weight and eating healthily can help protect your eyesight. Your general practitioner can help you with quitting smoking and losing weight.

The best things you can do to protect your eyesight is to follow your eye doctor's advice and to make sure you keep all of your scheduled appointments.

How is CRVO treated?

There are several treatment options for CRVO and they work in different ways.

Some of these treatments work by shrinking and sealing up these weak blood vessels to prevent them from becoming blocked. Other treatments focus on reducing swelling and managing pain.

Since no two people are alike, there is no one-size-fits-all solution. Your doctor will choose a treatment best-suited for your individual needs.

What is EYLEA®?

EYLEA is a type of treatment known as an anti-VEGF.

This is an abbreviation for anti-vascular endothelial growth factor, which is a description of how EYLEA works to protect your vision. EYLEA blocks a particular protein used to develop new blood vessels in your eye. By stopping this from happening, EYLEA can keep weak blood vessels from being made which in turn can help improve your eyesight or stop it from getting worse.

EYLEA is a solution (a liquid) that is injected into the eye. While it is understandable to worry about an injection, most people who have EYLEA treatment say that the injection is painless and it sounds worse than it really is.

Who is EYLEA® for?

EYLEA is for people who have been diagnosed with CRVO.

Before your EYLEA treatment starts, make sure to tell your doctor or nurse if you:

- Have an infection in or around your eye
- If you currently have redness in your eye or if there is any pain in your eye
- Think you may be allergic to iodine, any pain killers or any of the ingredients in EYLEA
- Have had any issues or problems with eye injections before
- Have glaucoma or a history of high pressure in your eye
- If you see, or have seen, flashes of light or ‘floaters’ in your vision
- Are taking any medications, with or without a prescription
- Are pregnant, planning to become pregnant or breastfeeding. There is no experience of using EYLEA in pregnant women. EYLEA should not be used during pregnancy, discuss this with your doctor before treatment with EYLEA. Women of child bearing potential should use effective contraception during their treatment and for at least three months after the last injection of EYLEA.
- Had or will have eye surgery within 4 weeks before or after EYLEA treatment

How can I get ready for my EYLEA® appointment?

Your doctor may ask you to take eye-drops for a few days before your appointment. After your treatment, your vision may be blurry so you should not drive home. Plan to have a friend or family member take you to your appointment or arrange another way to get there and home again. On the day of your appointment, do not wear any makeup.

What can I expect at my EYLEA appointment?

Your doctor or nurse will get you ready for your EYLEA treatment. These people are highly trained professionals with experience in treating CRVO. They understand that the treatment procedure may sound frightening and they will take extra care to make sure you are relaxed and comfortable.

You will be given eyedrops which act as a local pain killer and an eyewash will be used to clean your eye and the skin around it. Your face will be covered by a special drape and your eye will be held open. The local pain killer will blur your vision so you will not see the needle.

An experienced doctor will give the injection into the white of your eye. Most people say the injection is painless and some say they feel a slight pressure. The whole procedure may feel a bit uncomfortable, but is over in a few minutes.

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Living with CRVO

Being diagnosed with CRVO and experiencing problems with your eyesight can be an anxious time. It is normal to worry and feel uncertain about your future, but your diagnosis doesn't mean you can no longer live a full life. You can continue to enjoy family, friends and interests with some small changes. Some helpful adjustments include:

- Tell friends and family that you have CRVO and it affects your vision
- Use brighter lighting
- Organise your surroundings so everything has a place
- Carry and use flashlights and magnifying lenses when about
- Read large print books and newspapers and try audio books

For more helpful tips on living with CRVO, please see the information on support groups below.

Support for people with CRVO

Wherever you are and however much you are affected by CRVO, it is important to remember that you are not alone. It may be difficult to understand your diagnosis or to come to terms with it. Speaking to experts can help answer questions you may have, while speaking to others who are in, or have been in, a similar situation to yourself can help you come to terms with your diagnosis.
[Links to be added]

For this section refer to common page

Your guide to EYLEA®

The brochure has been produced for people who have been prescribed EYLEA (aflibercept solution for injection)

EYLEA is used to treat wet age-related macular degeneration (wAMD)

Welcome to your EYLEA guide

Your doctor has prescribed EYLEA because you have been diagnosed with wet age-related macular degeneration, wAMD. This is a condition that is making it harder for you to see clearly. Treatments like EYLEA can help stop your eyesight from becoming worse, and may improve some of the symptoms you have.

This booklet also contains an audio CD with all of the information contained in this book.

Whether you read this guide or choose to listen to it on CD, it has been made to help answer any questions you may have, so you can get the most out of your treatment.

Your eye care clinic is:

Contact:

Telephone:

Address:

Email:

Within this book you will find:

- Information to help you understand wAMD
    - What is wAMD?
    - What causes wAMD?
    - Advice for living with wAMD

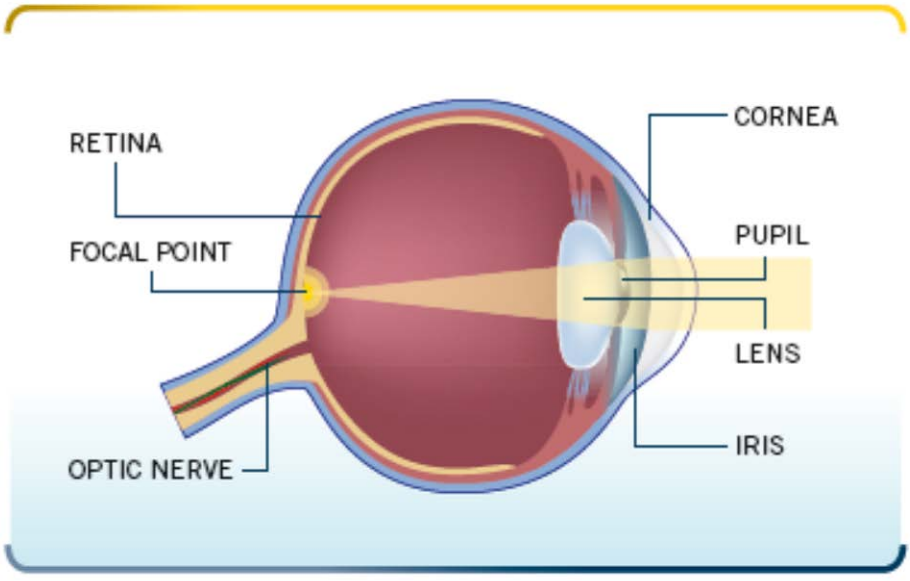
- What to expect from your EYLEA® treatment
    - What is EYLEA?
    - How will I take EYLEA?
    - What if I have questions about EYLEA?

- How to care for your eyes after your EYLEA treatment
    - What should I expect?
    - When do I need to take EYLEA again?
    - Are there side effects with EYLEA?

There is also useful information about support groups for wAMD and a calendar to help you keep track of your EYLEA treatment.

What is wAMD?

People with wAMD have an abnormal formation of new blood vessels in the eye. These weak blood vessels can cause the leak of fluid into the eye. The macula is the part of the retina responsible for central and fine vision. The leaked fluid can cause the central vision to become blurry and over time can create scars. Like scratches on a photograph, these scars make it harder for you to see all that you should.



What causes wAMD?

Wet age-related macular degeneration is as the name suggests, primarily caused by aging.

There are many factors, such as your age, your family history and genes, high blood pressure and cholesterol can all increase the risk of wAMD.

Other things that can increase your risk of getting wAMD, or having it get worse, are ‘lifestyle’ factors including smoking and being overweight. Quitting smoking greatly lowers the risk of damage to your eyes as well as improving your general health. If you are overweight, losing weight and eating healthily can help protect your eyesight. Your general practitioner can help you with quitting smoking and losing weight.

The best things you can do to protect your eyesight are to follow your eye doctor’s advice and to make sure you keep all of your scheduled appointments.

How is wAMD treated?

There are several treatment options for wAMD and they work in different ways. Some treatments work by stopping new, weak blood vessels from being made. Another way to treat wAMD is through laser surgery, which works by shrinking and sealing up these weak vessels that have already been made.
Since no two people are alike, there is no one-size-fits-all solution. Your doctor will choose a treatment best-suited for your individual needs.

What is EYLEA?

EYLEA is a type of treatment known as an anti-VEGF. This is an abbreviation for anti-vascular endothelial growth factor, which is a description of how EYLEA works to protect your vision. EYLEA blocks a particular protein that creates leaky blood vessels. This helps reduce the fluid that is leaked into the eye.

EYLEA is a solution (a liquid) that is injected into the eye. While it is understandable to worry about an injection, most people who have EYLEA treatment say that the injection is painless and it sounds worse than it really is.

Who is EYLEA for?

EYLEA is for people who have been diagnosed with wAMD.

Before your EYLEA treatment starts, make sure to tell your doctor or nurse if you:

- Have an infection in or around your eye
- If you currently have redness in your eye or if there is any pain in your eye
- Think you may be allergic to iodine, any pain killers or any of the ingredients in EYLEA
- Have had any issues or problems with eye injections before
- Have glaucoma or a history of high pressure in your eye
- If you see, or have seen, flashes of light or ‘floaters’ in your vision
- Are taking any medications, with or without a prescription
- Are pregnant, planning to become pregnant or breastfeeding. There is no experience of using EYLEA in pregnant women. EYLEA should not be used during pregnancy, discuss this with your doctor before treatment with EYLEA. Women of child bearing potential should use effective contraception during their treatment and for at least three months after the last injection of EYLEA
- Had or will have eye surgery within four weeks before or after EYLEA treatment

How can I get ready for my EYLEA appointment?

Your doctor may ask you to take eye-drops for a few days before your appointment. After your treatment, your vision may be blurry so you should not drive home. Plan to have a friend or family member take you to your appointment or arrange another way to get there and home again. On the day of your appointment, do not wear any makeup.

What can I expect at my EYLEA appointment?

Your doctor or nurse will get you ready for your EYLEA treatment. These people are highly trained professionals with experience in treating wAMD. They understand that the treatment procedure may sound concerning and they will take extra care to make sure you are relaxed and comfortable.

You will be given eye drops which act as a local pain killer and an eyewash will be used to clean your eye and the skin around it. Your face will be covered by a special drape and your eye will be held open. The local pain killer will blur your vision so you will not see the needle.

An experienced doctor will give the injection into the white of your eye. Most people say the injection is painless and some say they feel a slight pressure. The whole procedure may feel a bit uncomfortable, but is over in a few minutes.

For this section refer to common page

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Living with wAMD

Being diagnosed with wAMD and experiencing problems with your eyesight can be an anxious time. It is normal to worry and feel uncertain about your future, but your diagnosis doesn't mean you can no longer live a full life. You can continue to enjoy family, friends and interests with some small changes.

Some helpful adjustments include:

- Tell friends and family that you have wAMD and it affects your vision
- Use brighter lighting
- Organise your surroundings so everything has a place
- Carry and use a torch and magnifying lenses when about
- Read large print books and newspapers and try audio books

Support for people with wAMD

Wherever you are and however much you are affected by wAMD, it is important to remember that you are not alone. It may be difficult to understand your diagnosis or to come to terms with it. Speaking to experts can help answer questions you may have, and speaking to others who are in, or have been in, a similar situation to yourself can help you come to terms with your diagnosis.
[Links to be added]

For this section refer to common page

Your guide to EYLEA®

The brochure has been produced for people who have been prescribed EYLEA (aflibercept solution for injection)

EYLEA is used to treat Branch Retinal Vein Occlusion (BRVO)

Welcome to your EYLEA guide

Your doctor has prescribed EYLEA because you have been diagnosed with branch retinal vein occlusion, or BRVO. This is a condition that is making it harder for you to see clearly. Treatments like EYLEA can help stop your eyesight from becoming worse, and may improve some of the symptoms you have.

This booklet also contains an audio CD with all of the information contained in this book.

Whether you read this guide or choose to listen to it on CD, it has been made to help answer any questions you may have, so you can get the most out of your treatment.

Your eye care clinic is:

Contact:

Telephone:

Address:

Email:

Within this book you will find:

- Information to help you understand BRVO
    - What is BRVO?
    - What causes BRVO?
    - Advice for living with BRVO

- What to expect from your EYLEA® treatment
    - What is EYLEA?
    - How will I take EYLEA?
    - What if I have questions about EYLEA?

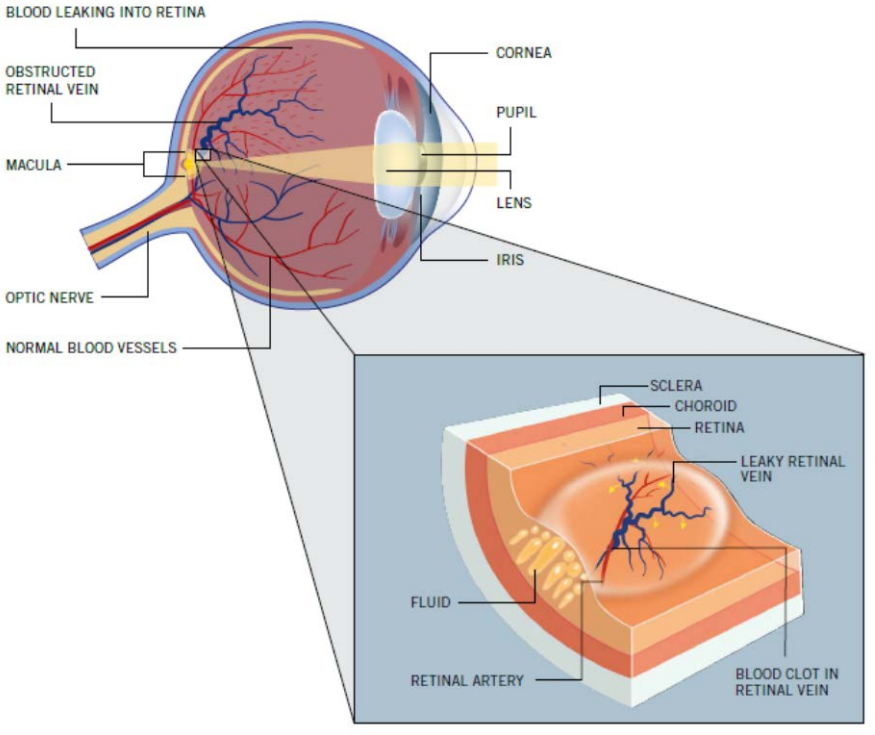
- How to care for your eyes after your EYLEA treatment
    - What should I expect?
    - When do I need to take EYLEA again?
    - Are there side effects with EYLEA?

There is also useful information about support groups for BRVO and a calendar to help you keep track of your EYLEA treatment.

What is BRVO ?

Within the back of your eye, there is a network of tightly woven cells and blood vessels that form a barrier to control substances entering or leaving your retina. The retina is where all of the images you see are recorded – it acts like the film in a camera.

People with BRVO have one or more branches of the blood vessels, that transport blood away from the retina, blocked. Fluid may then leak through causing swelling. The macula is the part of the retina responsible for central and fine vision. When the macula swells with fluid, central vision becomes blurry. Over time the swelling can create scars which damage the retina. Like scratches on a photograph, these scars make it harder for you to see all that you should.



What causes BRVO ?

In many people with BRVO, a specific cause can't be determined but it often happens as a consequence of other conditions like atherosclerosis (hardening of the arteries), glaucoma or diabetes.

Other things that can increase your risk of getting BRVO, or having it get worse, are 'lifestyle' factors including smoking, not exercising and being overweight. Quitting smoking greatly lowers the risk of damage to your eyes as well as improving your general health. If you are overweight, losing weight and eating healthily can help protect your eyesight. Your general practitioner can help you with quitting smoking and losing weight.

The best things you can do to protect your eyesight is to follow your eye doctor's advice and to make sure you keep all of your scheduled appointments.

How is BRVO treated ?

There are several treatment options for BRVO and they work in different ways. Generally, these treatments work by shrinking and sealing up the leaking blood vessels. These treatments can involve injections or laser surgery.

Since no two people are alike, there is no one-size-fits-all solution. Your doctor will choose a treatment best-suited for your individual needs.

What is EYLEA ?

EYLEA is a type of treatment known as an anti-VEGF. This is an abbreviation for anti-vascular endothelial growth factor, which is a description of how EYLEA works to protect your vision. EYLEA blocks a particular protein that creates leaky blood vessels. This helps reduce the swelling in the retina and protects your vision.

EYLEA is a solution (a liquid) that is injected into the eye. While it is understandable to worry about an injection, most people who have EYLEA treatment say that the injection is painless and it sounds worse than it really is.

Who is EYLEA for ?

EYLEA is for people who have been diagnosed with BRVO.

Before your EYLEA treatment starts, make sure to tell your doctor or nurse if you:

- Have an infection in or around your eye
- If you currently have redness in your eye or if there is any pain in your eye
- Think you may be allergic to iodine, any pain killers or any of the ingredients in EYLEA
- Have had any issues or problems with eye injections before
- Have glaucoma or a history of high pressure in your eye
- If you see, or have seen, flashes of light or ‘floaters’ in your vision
- Are taking any medications, with or without a prescription
- Are pregnant, planning to become pregnant or breastfeeding. There is no experience of using EYLEA in pregnant women. EYLEA should not be used during pregnancy, discuss this with your doctor before treatment with EYLEA. Women of child bearing potential should use effective contraception during their treatment and for at least three months after the last injection of EYLEA
- Had or will have eye surgery within four weeks before or after EYLEA treatment

How can I get ready for my EYLEA appointment ?

Your doctor may ask you to take eye-drops for a few days before your appointment. After your treatment, your vision may be blurry so you should not drive home. Plan to have a friend or family member take you to your appointment or arrange another way to get there and home again. On the day of your appointment, do not wear any makeup.

What can I expect at my EYLEA appointment ?

Your doctor or nurse will get you ready for your EYLEA treatment. These people are highly trained professionals with experience in treating BRVO. They understand that the treatment procedure may sound concerning and they will take extra care to make sure you are relaxed and comfortable.

You will be given eye drops which act as a local pain killer and an eye wash will be used to clean your eye and the skin around it. Your face will be covered by a special drape and your eye will be held open. The local pain killer will blur your vision so you will not see the needle.

An experienced doctor will give the injection into the white of your eye. Most people say the injection is painless and some say they feel a slight pressure. The whole procedure may feel a bit uncomfortable, but is over in a few minutes.

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Living with BRVO

Being diagnosed with BRVO and experiencing problems with your eyesight can be an anxious time. It is normal to worry and feel uncertain about your future, but your diagnosis doesn't mean you can no longer live a full life. You can continue to enjoy family, friends and interests with some small changes.

Some helpful adjustments include:

- Tell friends and family that you have BRVO and it affects your vision
- Use brighter lighting
- Organise your surroundings so everything has a place
- Carry and use a torch and magnifying lenses when about
- Read large print books and newspapers and try audio books

Support for people with BRVO

Wherever you are and however much you are affected by BRVO, it is important to remember that you are not alone. It may be difficult to understand your diagnosis or to come to terms with it. Speaking to experts can help answer questions you may have, and speaking to others who are in, or have been in, a similar situation to yourself can help you come to terms with your diagnosis.
[Links to be added]

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The following sections are common to ALL patient brochures / indications

What if I have concerns or questions?

If you have any concerns or questions, your doctor or nurse are the best people to speak to. They are very experienced and they know your individual situation so can provide you with the answers you need.

Don’t worry about asking questions or voicing any concerns. Your doctor or nurse can give you answers and reassurance.

What can I expect after my EYLEA® appointment?

Your doctor may give you some eye tests after your injection. This may include a puff of air that measures the pressure inside your eye. After your injection, your vision will be blurry so you should not plan to drive until after your vision returns to normal.

In the next few days you may get a bloodshot eye or see moving spots in your vision. Both of these should clear within a few days and if they don’t, or if they get worse, you should contact your doctor.

Some people might feel a little bit of pain or discomfort in their eye after their injection. If this does not go away or gets worse, you should contact your doctor.

When do I need to come back for another appointment?

Your doctor will arrange your next EYLEA appointment with you. Your treatment schedule will be created to best meet your individual needs.

Remember, your doctor or nurse is always the best person to speak to if you have questions about your treatment.

Speak with your doctor before stopping your EYLEA treatment.

When you get a new appointment, don’t forget to record it in the calendar on the back cover as a reminder.

Does EYLEA have side effects?

Just like any medicine, whether it is by prescription or over the counter, EYLEA has the potential to cause side effects. Not everyone who takes EYLEA will experience a side effect.

Side effects may include:

- Infection inside the eye: Eye pain or increased discomfort. Worsening eye redness, sensitivity to light, swelling and vision changes such as sudden decrease in vision or blurring of vision.
- Clouding of the lens (cataract): Seeing shadows, less vivid lines and shapes or less colour vision.
- Increase in eye pressure: Seeing halos around lights. Experiencing a red eye, nausea, vomiting and vision changes.
- Tear or detachment of a layer of the retina: Sudden flashes of light, a sudden appearance or an increase of floaters, a curtain like effect over a portion of the visual area, and vision changes.

Contact your doctor immediately if you think you have experienced any of these side effects.

For a full list of side effects, refer to your Patient Information Leaflet included with your patient brochure.

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[Notes section]

Back cover

[Calendar/appointment card]

Date of prep
Job number
Logo