Summary of Risk Management Plan for Eylea (aflibercept)

This is a summary of the EU risk management plan (RMP) for Eylea. The RMP details important risks of Eylea, how these risks can be minimized, and how more information will be obtained about Eylea's risks and uncertainties (missing information).

Eylea's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Eylea should be used.

This summary of the RMP for Eylea should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Eylea's RMP.

I. The medicine and what it is used for

Eylea is indicated for adults for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to macular edema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to diabetic macular edema (DME), and visual impairment due to myopic choroidal neovascularization (myopic CNV; see SmPC for the full indication). It contains aflibercept as the active substance and it is given by intravitreal injection. The following pharmaceutical form is currently available:

- Solution for injection in a vial. One vial contains 4 mg aflibercept in 100 microliters (40 mg/mL) in iso-osmotic solution. Delivers a single dose of 2 mg/0.05 mL.

Further information about the evaluation of Eylea's benefits can be found in Eylea's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Eylea, together with measures to minimize such risks and the proposed studies for learning more about Eylea's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Eylea, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Eylea is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Eylea are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Eylea. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g.; on the long-term use of the medicine).

Table II-1: List of important risks and missing information

Summary of safety concerns	
Important identified risks	• Endophthalmitis (likely infectious origin) • Intraocular inflammation • Transient intraocular pressure increase • Retinal pigment epithelial tears • Retinal tear / detachment • Cataract (especially of traumatic origin) • Hypersensitivity and immunogenicity
Important potential risks	• Arterial thromboembolic events including non-MI ATEs and cardiovascular ischemic events • Venous thromboembolic events • Hypertension • Proteinuria • Non-ocular hemorrhage • Medication errors • Off-label use and misuse • Embryo-fetotoxicity • Retinal hemorrhage
Missing information	• Use of Eylea in patients with uncontrolled glaucoma • Concomitant use of different anti-VEGF therapies and other therapies for wet AMD, CRVO, BRVO, myopic CNV, and DME. Concomitant use includes bilateral treatment with anti-VEGFs. • Long term safety beyond 2 years • Posology utilized in marketed use

II.B Summary of important risks

Table II-2: Important identified risk: Endophthalmitis (likely infectious origin)

Evidence for linking the risk to the medicine	The intravitreal injection procedure can implant pathogens into the eye if there is a break in sterile technique. Source of pathogenic agents is in most cases the patient's conjunctival bacterial flora.
Risk factors and risk groups	Improper aseptic technique increases the risk of intraocular inflammation.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.3, 4.4, and 4.8 Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video, patient booklet "Your guide to Eylea", patient information leaflet, and audio CD).
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table II-3: Important identified risk: Intraocular inflammation

Evidence for linking the risk to the medicine	Post-injection, sterile intraocular inflammation is a known risk following intravitreal injections of anti-VEGFs and for other intravitreally applied drugs.
Risk factors and risk groups	Improper aseptic technique increases the risk of intraocular inflammation.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.3, 4.4, and 4.8 Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video, patient booklet "Your guide to Eylea", patient information leaflet, and audio CD).
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table II-4: Important identified risk: Transient intraocular pressure increase (IOP)

Evidence for linking the risk to the medicine	Transient IOP increase is attributed to an increase in vitreous volume after Eylea injection (volume effect).
Risk factors and risk groups	To date no risk group is identified. Safety data in patients with uncontrolled glaucoma is missing.

Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.4, 4.8, and 4.9 Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video, patient booklet “Your guide to Eylea”, patient information leaflet, and audio CD).
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Follow-up survey to evaluate effectiveness of updated educational material (Study # 20285): protocol was submitted to EMA for review on 25 June 2018.

Table II-5: Important identified risk: Retinal pigment epithelial (RPE) tears

Evidence for linking the risk to the medicine	Development of RPE tears after anti-VEGF intravitreal injection has been attributed to a decline in intercellular adherence, thereby increasing susceptibility to tearing of the RPE layer particularly in patients with wet AMD.
Risk factors and risk groups	Wet AMD with pigment epithelial detachment; treatment of neovascularization.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video, patient booklet “Your guide to Eylea”, patient information leaflet, and audio CD).
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table II-6: Important identified risk: Retinal tear / detachment

Evidence for linking the risk to the medicine	Tractive forces in the inner eye may lead to tearing and detachment of the retina. In addition, the intravitreal injection procedure can, through the needle stick and movements, increase the tractive forces within a short period of time and thereby promote the development of retinal tear/detachment.
Risk factors and risk groups	Myopia, previous cataract surgery, glaucoma, severe injury, previous retinal detachment in your other eye, family history of retinal detachment, IVT injections.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 Additional risk minimization measures:

	None, since routine risk minimization activities are considered sufficient.

Table II-7: Important identified risk: Cataract (especially of traumatic origin)

Evidence for linking the risk to the medicine	Related to IVT procedure.
Risk factors and risk groups	IVT corticosteroids, diabetes mellitus, lens trauma.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video, patient booklet “Your guide to Eylea”, patient information leaflet, and audio CD).
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table II-8: Important identified risk: Hypersensitivity and immunogenicity

Evidence for linking the risk to the medicine	Hypersensitivity reactions may be observed with any medication; including Eylea.
Risk factors and risk groups	No risk factors identified.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.3, 4.4, and 4.8 Additional risk minimization measures: None, since routine risk minimization activities are considered sufficient.

Table II-9: Important potential risk: Arterial thromboembolic events including non-MI ATEs and cardiovascular ischemic events

Evidence for linking the risk to the medicine	Systemic treatment with VEGF inhibitors (at much higher doses than with IVT administration) is known to increase the risk of ATEs. VEGF increases the production of nitric oxide (NO) and prostacyclin (PGI2). Reduction of PGI2 and NO by inhibition of VEGF signaling may predispose to thromboembolic events. VEGF inhibition may also increase risk of thrombosis by increasing hematocrit and blood viscosity via overproduction of erythropoietin. Due to the low systemic exposure, systemic pharmacodynamic effects, including the development of ATEs, are deemed unlikely.
Risk factors and risk groups	Generally, risk factors for arterial thromboembolic events (ATEs) are diabetes mellitus, hypertension, smoking, obesity, hyperlipidemia, atrial fibrillation, older age and patient or family history.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 Additional risk minimization measures: None

Table II-10: Important potential risk: Venous thromboembolic events

Evidence for linking the risk to the medicine	Systemic anti-VEGF treatment might affect the vascular integrity.
Risk factors and risk groups	Immobilization, older age, Factor V Leiden mutation, protein S or protein C deficiency, venous insufficiency, smoking, hyperlipidemia, cancer, anti-phospholipid syndrome, surgery.
Risk minimization measures	Routine risk minimization measures: None Additional risk minimization measures: None

Table II-11: Important potential risk: Hypertension

Evidence for linking the risk to the medicine	Different potential mechanisms are discussed: Inhibition of VEGF in arterial endothelial cells by systemically administered VEGF inhibitors may decrease the release of nitric oxide (NO), which acts on arterial smooth muscle cells to cause vasodilation. A decrease in NO results in the dominance of vasoconstrictive factors on the peripheral vascular beds. As VEGF is involved in the control of glomerular capillary function, systemic VEGF inhibition could cause an increase in systemic vascular resistance through affecting the renin-angiotensin-system, and it could also induce a thrombotic microangiopathy in the kidneys vessels leading to imbalances in blood pressure levels. Evidence exists to show that chronic systemic VEGF inhibition causes capillary rarefaction (decrease in number of capillaries), both in preclinical models and in humans. This capillary rarefaction may increase afterload and thereby contribute to the pathophysiology of hypertension induced by systemic VEGF inhibition.
Risk factors and risk groups	Hyperlipidemia, obesity, smoking, renal artery stenosis.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 Additional risk minimisation measures: None

Table II-12: Important potential risk: Proteinuria

Evidence for linking the risk to the medicine	Physiological levels of VEGF are known to significantly regulate the glomerular and tubular capillary network. Systemic exposure to an anti-VEGF agent may result in structural changes of the filtration barrier of the renal glomeruli. Low levels of physiological circulating VEGF inhibit the interaction of endothelial cells and podocytes in glomerular capillaries, leading to damage in the filtration barrier, subsequently causing proteinuria.
Risk factors and risk groups	Chronic kidney diseases
Risk minimization measures	Routine risk minimization measures: None Additional risk minimization measures: None

Table II-13: Important potential risk: Non-ocular hemorrhage

Evidence for linking the risk to the medicine	Inhibition of VEGF seemingly diminishes the regenerative capacity of endothelial cells, and increases vascular fragility. The VEGF pathway also interacts closely with other various cytokines as metalloproteinases which target tissue remodeling. Nevertheless, in the case of systemic VEGF therapy for treatment of malignancy, the risk of bleeding may be confounded by thrombocytopenia, generally associated with the concomitant use of myelosuppressive cytotoxic agents, in addition to the occurrence of local bleeding due to localized tumor necrosis at a critical site. VEGF is normally concentrated in endothelial cells and connective tissue of intestinal mucosa, to promote angiogenesis as a part of connective tissue repair following any mucosal injury. VEGF plays also an important role in the healing process of stress induced peptic ulcer.
Risk factors and risk groups	Anticoagulation/anti platelet therapies, thrombocytopathy, coagulopathy, malignancy, vasculopathy, older age, surgery, trauma.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 Additional risk minimization measures: None, since routine risk minimization activities are considered sufficient.

Table II-14: Important potential risk: Medication errors and misuse

Evidence for linking the risk to the medicine	Although Eylea is provided in a pre-filled syringe, there is an excess volume which exceeds the recommended net dose of 2 mg Eylea per injection. Thus, injecting the entire volume of the pre-filled syringe would result in overdose. However, this numerical overdose is limited, and the drug will be administered only by qualified physicians (not by patients), and this reduces the risk of inappropriate dosing and administration as well. No clinically meaningful events of overdose have been reported so far (neither in clinical trials nor in usual care). Nevertheless, it was decided to consider "medication error" a potential risk of treatment, which is, however, completely avoidable by proper adherence to the dosing recommendations.
Risk factors and risk groups	Not applicable
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.9 and 6.6 Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise physicians' awareness on medication error (prescriber guide and video, patient booklet “Your guide to Eylea”, patient information leaflet, and audio CD).

Table II-14: Important potential risk: Medication errors and misuse

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Follow-up survey to evaluate effectiveness of updated educational material (Study # 20285): was submitted to EMA for review on 25 June 2018.

Table II-15: Important potential risk: Off-label use

Evidence for linking the risk to the medicine	As with other drugs, Eylea might be intentionally used other than recommended, or in clinical conditions outside the approved indications (so-called off-label use). Since the clinical experience with Eylea in such off-label use will be limited (in particular in terms of efficacy and safety), any case of off-label use will be considered a potential risk. Since Eylea has no dependence potential, the risk of misuse is regarded as very low.
Risk factors and risk groups	Not applicable
Risk minimization measures	Routine risk minimization measures: Provision of entire SmPC, in which the approved use of Eylea is detailed. Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on off-label use (prescriber guide and video, patient booklet “Your guide to Eylea”, patient information leaflet, and audio CD).
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.

Table II-16: Important potential risk: Embryo-fetotoxicity

Evidence for linking the risk to the medicine	An embryo-fetal toxicity study was performed in the rabbit with IV dosing of aflibercept at doses which provided systemic exposures over 670-fold higher than that observed with IVT dosing using the clinical dose of 2 mg. The study identified dose-related increases in fetal resorptions, pregnancy disruptions and numerous fetal (external, visceral and skeletal) malformations. These effects were thought to be due to the antiangiogenic effect of aflibercept.
Risk factors and risk groups	Patients at risk are women of child bearing potential.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.6 Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on the potential risk of embryo-toxicity and the need for appropriate contraception in women of childbearing potential (prescriber guide and video, patient booklet "Your guide to Eylea", patient information leaflet, and audio CD).
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Follow-up survey to evaluate effectiveness of updated educational material (Study # 20285): protocol was submitted to EMA for review on 25 June 2018.

Table II-17: Important potential risk: Retinal haemorrhage

Evidence for linking the risk to the medicine	Retinal bleeding is a condition where blood effuses from the retinal blood vessels into the surrounding retinal tissue. Many ocular diseases, including wet AMD, CRVO, BRVO, or DME may lead to retinal bleeding. However, since rare cases of retinal hemorrhages were reported to be related to intravitreal treatment with anti-VEGF therapies, this condition is also considered a potential risk.
Risk factors and risk groups	Wet AMD, CRVO, DME, BRVO retinal neovascularization, anticoagulant/antiplatelet therapy, older age, and hypertension.
Risk minimization measures	Routine risk minimization measures: None Additional risk minimization measures: None

Table II-18: Missing information: Use of Eylea in patients with uncontrolled glaucoma

Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 Additional risk minimization measures: None

Table II-19: Missing information: Concomitant use of different anti-VEGF therapies and other therapies for wet AMD, CRVO, BRVO, myopic CNV and DME. Concomitant use includes bilateral treatment with anti-VEGFs.

Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.5 Additional risk minimization measures: None

Table II-20: Missing information: Long term safety beyond 2 years

Risk minimization measures	Routine risk minimization measures: None Additional risk minimization measures: None

Table II-21: Missing information: Posology utilized in marketed use

Risk minimization measures	Routine risk minimization measures: None Additional risk minimization measures: None

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

The following studies are conditions of the marketing authorization:

Study short name: AZURE, BAY 86-5321/16598

Study no. BAY 86-5321/16598: An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of 2 mg Eylea administered by intravitreal injections using two different treatment regimens to subjects with neovascular age-related macular degeneration (wet AMD)

Purpose of the study:

To compare the efficacy, safety, and tolerability of 2 mg Eylea administered by two different intravitreal (IVT) treatment regimens to subjects with nAMD.

As a condition for approval, the European Medicines Agency (EMA) has required a study to assess every-other-month dosing versus an extended-dosing regimen with no maximum limit to the treatment interval.

Study short name: VIOLET, BAY 86-5321/17613

Study no. BAY 86-5321/17613: A randomized phase 3b study comparing 3 dosing regimens of intravitreal VEGF Trap-Eye in patients with diabetic macular edema.

Purpose of the study:

The aim is to perform an interventional post-authorization efficacy study in patients with diabetic macular edema with the primary objective to assess whether treatment according to label, i.e., extended treatment intervals based on visual and anatomic outcomes (“treat and extend”) and PRN treatment after at least one year of Eylea treatment according to label is non-inferior to the studied treatment regimen of a fixed dosing every two months (2Q8).

Table II-22: Studies which are conditions of the marketing authorization

Study Status	Summary of objectives	Safety concerns/efficacy issue addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization *(key to benefit risk)*				
An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of 2 mg Eylea administered by intravitreal injections using two different treatment regimens to subjects with neovascular age-related macular degeneration (wet AMD) (330 patients) Status: Ongoing	• Primary study objective: To compare the efficacy of 2 mg Eylea administered by two different intravitreal (IVT) treatment regimens to subjects with wet AMD. • Safety and tolerability.	• As a condition for approval, the European Medicines Agency (EMA) has required a study to assess every-other-month dosing versus an extended-dosing regimen with no maximum limit to the treatment interval.	Approved by EMA in OCT 2014, first patient screened in Q3 2015.	Submission of final CSR planned for 30 NOV 2021
A randomized phase 3b study comparing 3 dosing regimens of intravitreal VEGF Trap-Eye in patients with diabetic macular edema. (490 patients) Status: Ongoing	• Primary study objective: To assess whether treatment according to label, i.e., extended treatment intervals based on visual and anatomic outcomes ("treat and extend") and PRN treatment after at least one year of Eylea treatment according to label is non-inferior to the studied treatment regimen of a fixed dosing every two months (2Q8). • Safety and tolerability.	• Evaluation of the possibility to extend treatment beyond 2Q8 without impact on efficacy.	Protocol endorsed by EMA in November 2015	Interim study report submission planned after 2nd year completion (in 2018) Final CSR in November 2019

Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations.
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimization measures).

II.C.2 Other studies in post-authorization development plan

Study short name: Study #20285

Follow-up survey to evaluate effectiveness of updated educational material (Study # 20285; Category 3)

Table II-23: Other studies in post-authorization development plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities *(by the competent authority)*				
Follow-up survey to evaluate effectiveness of updated educational material for HCPs (Study # 20285) (PASS) Status: submitted	• To evaluate the level of physicians' knowledge and understanding of key safety Information contained in the prescriber guide especially on use during pregnancy, evaluation of vision and monitoring IOP post injection, and reuse of the vial.	• Transient Intraocular pressure increase (evaluation of vision and monitoring of IOP post- injection) • Embryofetotoxicity (use during pregnancy) • Medication error • and misuse (identify potential misuse, including reuse of the vial)	Protocol submission Study start Study report submission	25 June 2018 Estimated August 2019. Estimated April 2021

Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations.
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimization measures).