Summary of the Risk Management Plan for Eylea®

Active substance: Aflibercept

Version number: version 3.0

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Based on the EU-RMP v33.4 for Eylea® (dated 12 OCT 2023)

Eylea®
(Aflibercept)
Risk Management Plan

Summary of activities in the risk management plan

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Eylea is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Eylea in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Bayer (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Eylea.

The Summary of the Risk Management Plan for Eylea v3.0 is based on the Summary of Activities in the Risk Management Plan by Product for Eylea (Aflibercept) of the EU-RMP v33.4, dated 12 OCT 2023. Deviations in the risk minimization measures applicable for Switzerland from the EU-RMP are possible.

Summary of Activities in the Risk Management Plan by Product

This is a summary of the EU risk management plan (RMP) for Eylea 40 mg/mL (2 mg dose), Eylea 40 mg/mL (0.4 mg dose), and Eylea 114.3 mg/mL (8 mg dose). 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 40 mg/mL (0.4/2 mg dose) and Eylea 114.3 mg/mL (8 mg dose) summary of product characteristics (SmPC) and their package leaflets 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.

1. The Medicine and what it is used for

Eylea 40 mg/mL (2 mg dose) 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).

Eylea 114.3 mg/mL (8 mg dose) is indicated for the treatment of wet AMD and DME (see SmPC for the full indication).

It contains aflibercept as the active substance and it is given by intravitreal injection. The following pharmaceutical forms are currently available:

- Eylea 40 mg/mL (2 mg dose): Solution for injection in a vial. One vial contains 4 mg aflibercept in 100 microliters in iso-osmotic solution. Delivers a single dose of 2 mg/0.05 mL.
- Eylea 40 mg/mL (2 mg dose): Solution for injection in a pre-filled syringe. One pre-filled syringe contains 3.6 mg aflibercept in 90 microliters in iso-osmotic solution. Delivers a single dose of 2 mg/0.05 mL.
- Eylea 114.3 mg/mL (8 mg dose): Solution for injection in a vial. One vial contains 11.4 mg aflibercept in 100 microlitres in iso-osmotic solution. Delivers a single dose of 8 mg/0.07 mL.

In addition, Eylea 40 mg/mL is indicated in premature infants for the treatment of retinopathy of prematurity (ROP). The dosing device PICLEO in combination with the pre-filled syringe and a low dead space needle are used for administration of a single dose of 0.4 mg aflibercept (equivalent to 0.01 mL solution for injection).

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 (https://www.ema.europa.eu/en/medicines/human/EPAR/eylea).

2. 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 analysed, 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.

2.1 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 Part 2.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	- Endophthalmitis (likely infectious origin) - Intraocular inflammation - Transient intraocular pressure increase - Retinal pigment epithelial tears - Cataract (especially of traumatic origin)
Important potential risks	- Medication errors - Off-label use and misuse - Embryo-fetotoxicity
Missing information	- Long-term safety of aflibercept in preterm infants with ROP - Exposure with bilateral 8 mg aflibercept therapy

2.2 Summary of Important Risks Eylea 40 mg/mL (0.4/2 mg doses) and Eylea 114.3 mg/mL (8 mg dose)

Important identified risk: Endophthalmitis (likely infectious origin)	
Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature. 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 Package Leaflet (for adults and babies born prematurely) sections 2, 3 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections.

Summary of activities in the risk management plan

Important identified risk: Endophthalmitis (likely infectious origin)	
	Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ (for adults) and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, for adult indications patient guide “Your guide to Eylea”, and its audio version).

Important identified risk: Intraocular inflammation	
Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature. 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 Package Leaflet (for adults and babies born prematurely) section 2, 3 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ (for adults) and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, for adult indications patient guide “Your guide to Eylea”, and its audio version).

Summary of activities in the risk management plan

Important identified risk: Transient intraocular pressure increase	
Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature. Transient IOP increase is attributed to an increase in vitreous volume after Eylea injection (volume effect).
Risk factors and risk groups	Patients with glaucoma. Increased intraocular pressure is a known adverse drug reaction on treatment with intravitreal corticosteroids.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.4, 4.8, and 4.9 Package Leaflet (for adults and babies born prematurely) sections 2 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ (for adults) and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, for adult indications patient guide “Your guide to Eylea”, and its audio version).

Important identified risk: Retinal pigment epithelial tears	
Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature. 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.

Summary of activities in the risk management plan

Important identified risk: Retinal pigment epithelial tears	
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 Package Leaflet sections 2 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational program for adults: 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 guide "Your guide to Eylea", and its audio version).

Important identified risk: Cataract (especially of traumatic origin)	
Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature. Related to IVT procedure.
Risk factors and risk groups	Cataract is a known adverse drug reaction on treatment with IVT corticosteroids.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.4 and 4.8 Package Leaflet sections 2, 3 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections.

Summary of activities in the risk management plan

Important identified risk: Cataract (especially of traumatic origin)	
	Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ (for adults) and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, for adult indications patient guide “Your guide to Eylea”, and its audio version).

Important potential risk: Medication errors	
Evidence for linking the risk to the medicine	Although 2mg 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. The drug will be administered only by qualified physicians (not by patients), and this reduces the risk of inappropriate dosing and administration as well. Proper adherence to the instructions for adequate PFS preparation and use minimizes medication errors.
Risk factors and risk groups	Not applicable
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.9 and 6.6 Package Leaflet section 1 and 3 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections. 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; in addition, for adult indications patient guide “Your guide to Eylea”, and its audio version).

Summary of activities in the risk management plan

Important potential risk: Off-label use and misuse	
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: SmPC section 4.1, 4.3, 4.4 and 4.6 Package Leaflet sections 1, 2 and 3 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' (for adults) and physicians' awareness on off-label use (prescriber guide and video; in addition for adult indications patient guide “Your guide to Eylea”, and its audio version).

Summary of activities in the risk management plan

Important potential risk: Embryo-fetotoxicity	
Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature. 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 childbearing potential.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4, 4.6 and 5.3 Package Leaflet section 2 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational program for adults: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on the potential risk of embryo-toxicity and to underline information on treatment of women of child-bearing potential, and the need for appropriate contraception in women of childbearing potential (prescriber guide and video, patient guide “Your guide to Eylea”, and its audio version).

Missing information: Long-term safety of aflibercept in preterm infants with ROP	
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 Additional risk minimization measures: None

Missing information: Exposure with bilateral 8 mg aflibercept therapy	
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 5.1 Additional risk minimization measures: None

3. Post-authorisation Development Plan

3.1 Studies which are conditions of the Marketing Authorization

No Category 1 studies are currently planned or ongoing which are the requisites of market authorization.

3.2 Other Studies in Post-authorization Development Plan

One Category 3 study (FIREFLEYE NEXT Phase IIIb study) is currently ongoing as additional pharmacovigilance activity to evaluate long-term safety of aflibercept (0.4 mg) in preterm infants with ROP.