EU Risk Management Plan

Eyluxvi

(aflibercept)

RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data lock point for this RMP: 12 Jun 2025

Rationale for submitting an updated RMP: Not applicable for initial marketing authorisation application submission

Summary of significant changes in this RMP: Not applicable for initial marketing authorisation application submission

Date of final sign-off: 29 Jul 2025

QPPV name: Winrich Rauschning, MD

QPPV signature: This RMP has been written and approved by the marketing authorisation applicant´s QPPV. The signed version is available on file.

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Part I: Product Overview

Table Part I.1 – Product Overview

Active substance (INN)	Aflibercept
Pharmacotherapeutic group(s) (ATC Code):	Antineovascularisation agents S01LA05
Marketing Authorisation Holder or Applicant:	Biolitec Pharma Limited Zweigniederlassung Jena Otto Schott Str 15 D 07745 Jena Germany
Medicinal products to which this RMP refers:	1
Invented name(s) in the European Economic Area (EEA)	Eyluxvi
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class Aflibercept is a recombinant fusion protein consisting of portions of human VEGF (Vascular Endothelial Growth Factor) receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1. It is a specific blocker that binds and inactivates VEGF and the related molecule, placental growth factor (PlGF). Summary of mode of action It is designed to interfere with the increase in vascular permeability and growth of pathological new blood vessels that lead to retinal oedema, ischemia and haemorrhage in diseases accompanied by ocular neo-vascularisation. Important information about its composition: Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.
Hyperlink to the Product Information	Refer Module 1.3.1 for Product Information

Indication(s) in the EEA	Current: initial marketing authorisation application submission Proposed: • 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) • Visual impairment due to myopic choroidal neovascularisation (myopic CNV)
Dosage in the EEA	Current: initial marketing authorisation application submission
	Proposed: 2 mg aflibercept per eye
Pharmaceutical form(s) and strengths	Current: initial marketing authorisation application submission
	Proposed: Solution for injection in a vial, 40 mg/mL
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Eyluxvi is an aflibercept biosimilar medicinal product to Eylea (EU/1/12/797/002), the reference medicinal product was named VEGF Trap-Eye during the development programme.

Part II: Module SI - Epidemiology of the indications and target populations

Not applicable since Eyluxvi is a biosimilar medicinal product.

Part II: Module SII - Non-clinical part of the safety specification

A comprehensive toxicology and safety pharmacology programme was conducted to support the clinical use as well as the initial marketing authorisation of the reference product aflibercept (Eylea EU/1/12/797). The monkey was identified as the only relevant species for repeated-dose studies with intravitreal (IVT) administration. This module summarises the relevant non-clinical findings. As an overall conclusion, none of the non-clinical findings are considered a safety concern for aflibercept requiring risk.

Repeat-dose toxicity

Repeated monthly IVT administration of aflibercept to monkeys for up to 8 months was not associated with ocular effects considered adverse. Ocular findings were limited to inflammation that was generally mild and reversed completely or mostly by 4-weeks post-dose.

Erosions and ulcerations of the respiratory epithelium of the nasal turbinates were observed in individual animals treated at and above the clinical dose of 2 mg/eye and with mostly low severity (exception: 1 animal with moderate, one with marked severity) at the end of the dosing period. However, assessing adverse events in clinical trials on adult patients including a substudy of one of the pivotal phase III studies (VIEW 2), serial nasal endoscopy and ears/nose/throat (ENT) specialist examinations of patients did not reveal any occurrence of these findings following repeated aflibercept IVT dosing.

Since preterm infants with ROP have lower safety margins and could be more sensitive than adult patients regarding changes of the nasal epithelium after IVT treatment with aflibercept, monitoring for nasal bleeding was included in the Phase III Study 20090 (FIREFLEYE). No cases of nasal bleeding were observed in this study in ROP aflibercept treated patients.

The target-organ toxicities observed after systemic administration of aflibercept occurred at exposures well exceeding the exposures achieved after IVT administration in adult patients and are, therefore, not considered relevant for the intravitreal use of aflibercept in this patient population. The above clinical data of the ENT substudy resolved the possibly remaining concerns for adult patients. Target organs, which appeared already at the LOAEL of the studies with systemic administration were especially the kidneys, the growth plates of the bones, and the nasal cavities/sinuses. Due to the above-mentioned reasons, the Phase III Study 20090 (FIREFLEYE) included monitoring for nasal bleeding, proteinuria and growth. No effects on these parameters were observed. Since the development of many organ systems, such as the kidney or the skeleton, continues in a preterm infant, growth and development of ROP patients enrolled in the clinical study will be monitored for a prolonged follow-up period to 5 years of age by enrolment into a long-term follow-up study (FIREFLEYE NEXT, extension study 20275).

Reproductive and developmental toxicity

Effects on male and female fertility were assessed as part of the 6-month studies in monkeys with intravenous (IV) administration of aflibercept at doses ranging from 3 to 30 mg/kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. Based on maximum concentration (C_{max}) and area under the concentration time curve (AUC) for free aflibercept observed at the 3 mg/kg IV dose, the systemic exposures were approximately 4,900-fold and 1,500-fold higher, respectively, than the exposures observed in adult patients after IVT administration of 2 mg and are, therefore, considered not relevant for the intravitreal use of aflibercept. All changes were reversible.

No changes to reproductive organs were observed after IVT administration of aflibercept in monkeys.

Based on its mechanism of action, aflibercept is expected to influence embryo-fetal development. This was shown in an embryo-fetal development study in pregnant rabbits with IV administration (3 to 60 mg/kg). At 60 mg/kg fetal resorptions, pregnancy disruptions and numerous fetal (external, visceral and skeletal) malformations were observed. The maternal "No Observed Adverse Effect Level" (NOAEL) was the dose of 3 mg/kg, whereas the developmental NOAEL was not identified, since at 3 mg/kg still some signs of embryo-fetal toxicity were observed in one fetus. At the lowest dose of 3 mg/kg, systemic exposures of free aflibercept were approximately 600- to 2,000-fold more than the maximum human exposure in adult patients after an IVT administration of 2 mg (based on AUC and C_{max}, respectively).

In a combined early embryonic / embryo-fetal development study with aflibercept in pregnant rabbits with subcutaneous (SC) administration (0.1 to 1 mg/kg) starting at gestation day (GD) 1, no influence on maternal toxicity, gestation rate, post-implantation loss, placental weight, placental appearance, fetal sex distribution, or fetal weight was observed at all doses tested. The overall rate of cardiac ventricular septal defects (with/without malformation of major vessels), and skeletal malformations was slightly higher in aflibercept treated than control animals but showed no clear dose-dependency. A "spina bifida" was seen in a single fetus from each of 2 different dams that received 0.1 mg/kg during gestation. A "meningocele" was seen in 1 fetus from a single dam that received 1.0 mg/kg during gestation. Based on the results of this study, the maternal NOAEL was 1 mg/kg. The developmental NOAEL was not identified. Comparison of the systemic exposures observed in this study with mean exposures observed in adult patients following a 2 mg/eye dose indicate an exposure margin of approximately 10-fold (based on mean AUC for free aflibercept).

These data support that treatment with aflibercept is not recommended during pregnancy unless the potential benefit outweighs the potential risk to the fetus. Likewise, aflibercept is not recommended in women of childbearing potential not using contraception.

The malformations and variations observed in the embryo-fetal development studies on aflibercept develop early in organogenesis whilst in preterm infants with ROP, development of the affected organ systems is already completed. Therefore, similar effects are not expected to occur after IVT treatment of these patients with aflibercept. Overall, from these data, there were no undue risks identified for the IVT treatment of premature infants presenting with ROP.

Organ toxicity (Nephro-/Hepatotoxicitv)

No signals indicating a potential for nephro- or hepatotoxicity were observed following intravitreal administration.

Genotoxicity

In accordance with International Council for Harmonisation (ICH) guideline S6, no genotoxicity studies were conducted. Since aflibercept is a large molecule, it is not expected to interact directly with deoxyribonucleic acid (DNA) or other chromosomal material.

Carcinogenicity

No studies explicitly targeting carcinogenicity were conducted. Based on studies performed so far, there is no evidence that aflibercept (or other VEGF-inhibitory compounds) act as growth factors or are immunosuppressive. Therefore, currently there is no reason to suspect that aflibercept has a tumorigenic potential.

General safety pharmacology / Drug interactions

Effects of aflibercept on blood pressure and wound healing were only observed following systemic administration. Exposures after systemic administration were substantially above those following IVT injection. Therefore, IVT administration of aflibercept is not expected to exert appreciable effects on VEGF-mediated processes outside of the eye of adult patients.

Since no overlapping substrate specificity in the metabolism of aflibercept and potentially co-administered small molecule drugs is expected, no drug interaction studies have been performed.

Conclusions on non-clinical data

The following conclusions can be derived from the non-clinical data outlined above:

No important identified risks (confirmed by clinical data) were identified.

The non-clinical safety studies performed in monkeys and rabbits with systemic administration of aflibercept, suggest a potential of aflibercept to impair fertility and to exert embryo- fetotoxic effects. However, the systemic exposure to free aflibercept in these models was distinctly higher than the exposure observed in adult patients following intravitreal injection of 2 mg. Overall, aflibercept should not be administered during pregnancy, unless the potential benefit outweighs the potential risk to the fetus, and aflibercept is not recommended in women of childbearing potential not using effective contraception during treatment and for at least 3 months after the last dose. Clinical data on this issue are currently not available. The occurrence of embryo-fetotoxicity (regarded as important potential risk) is an objective of routine pharmacovigilance monitoring. The effects on the developing embryo/fetus observed in the embryo-fetal development studies occur early in organogenesis.

Erosions and ulcerations of the respiratory epithelium of the nasal turbinates, which were observed in individual monkeys in a repeat-dose IVT study, were not confirmed in a targeted sub-study within the clinical phase III study VIEW 2. In the Phase III Study 20090 (FIREFLEYE) in preterm infants with ROP, monitoring for nasal bleeding was included, since this patient population could be more sensitive regarding changes of the nasal epithelium after IVT treatment with aflibercept and have a higher systemic exposure than adults. No cases of nasal bleeding were observed in this study.

Due to the low systemic exposure following the IVT route of administration, aflibercept is generally not expected to exert appreciable effects on VEGF-mediated processes outside of the eye. To confirm this also in preterm infants with ROP, target organs like the kidneys, growth plates of the bones, and the nasal cavities / sinuses, which appeared already at the LOAEL of the toxicological studies with systemic administration, were included in the monitoring of the Phase III Study 20090 (FIREFLEYE). No cases of nasal bleeding, proteinuria and no effects on growth were observed in this study.

No signs of hepatotoxicity or nephrotoxicity in nonclinical toxicology programme were observed.

Studies focusing on genotoxicity, carcinogenicity, or drug interactions were not performed, since such endpoints are not applicable to the drug or are not relevant for IVT treatment. Blood pressure increases were observed after systemic administration of aflibercept in safety pharmacology studies in rodents. Since safety margins are low for this parameter in preterm infants, blood pressure was monitored in the Phase III Study 20090 (FIREFLEYE). No correlation between change in blood pressure and concentrations of free aflibercept was observed in this study.

Part II: Module SIII - Clinical trial exposure

SIII.1 Brief overview of development

Eyluxvi (international non-proprietary name: aflibercept) was developed by Alteogen Inc. and Altos Biologics Inc. as a biosimilar biological medicinal product to Eylea (EU/1/12/797/002).

SIII.2 Clinical Trial exposure of Eyluxvi

The clinical development programme of Eyluxvi consists of two trials comparing the biosimilar to Eylea, a phase I trial with 14 patients treated with Eyluxvi and a phase III trial with 216 patients summing up to 230 patients in total. 229 patients were treated with Eylea in the control arms (14+215 patients).

Study ALT-L9-01, a phase I first in human Eyluxvi study (Aflibercept) evaluated the safety, efficacy and pharmacokinetics of Eyluxvi in comparison to Eylea in patients with neovascular (wet) AMD. To be eligible for this study, patients were to have received prior anti-VEGF treatment for wet AMD in the study eye but at least 8 weeks prior to the baseline visit. 14 patients were treated in each group.

Study ALT-L9-03 (ALTERA), a randomised, Phase III, double-masked, parallel-group, multicentre study compared the efficacy, safety, pharmacokinetics and immunogenicity of Eyluxvi to Eylea in wet AMD patients. 216 patients were treated with Eyluxvi and 215 patients were treated with Eylea.

Part II: Module SIV - Populations not studied in clinical trials

As aflibercept belongs to the class of potentially teratogenic anti-VEGF therapies, embryo-fetotoxicity has been identified as an important potential risk. No additional safety concerns were identified in the clinical development of aflibercept. The use of aflibercept in patients with uncontrolled glaucoma and the concomitant use of different anti-VEGF therapies and other therapies for wet AMD, CRVO, BRVO, myopic CNV, and DME (including bilateral treatment) are regarded as missing information (Pospisil 2024).

Part II: Module SV - Post-authorisation experience

Not applicable for Eyluxvi since this is the initial application for marketing authorisation.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

No potential for misuse or illegal purposes is currently anticipated with the use of aflibercept.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

The following treatment-emergent drug reactions (reported in patients in aflibercept Phase III studies of the reference product (development name VEGF Trap-Eye) and confirmed in the clinical study of Eyluxvi are included in the proposed SmPC:

Very common: Visual acuity reduced, conjunctival haemorrhage, eye pain.

Common: Retinal pigment epithelial tear, detachment of retinal pigment epithelium, retinal degeneration, vitreous haemorrhage, cataract, cataract cortical, cataract nuclear, cataract subcapsular, corneal erosion, corneal abrasion, intraocular pressure increased, vision blurred, vitreous floaters, vitreous detachment, injection site pain, foreign body sensation in eyes, lacrimation increased, eyelid oedema, injection site haemorrhage, punctate keratitis, conjunctival hyperaemia, ocular hyperaemia.

Uncommon: Hypersensitivity, endophthalmitis, retinal detachment, retinal tear, iritis, uveitis, iridocyclitis, lenticular opacities, corneal epithelium defect, injection site irritation, abnormal sensation in eye, eyelid irritation, anterior chamber flare, corneal oedema.

Rare: Blindness, traumatic cataract, vitritis, hypopyon.

The conditions, which are regarded as important identified or potential risks (either as single preferred term event term or by term grouping) are underlined in the preceding listing. The remaining risks are not regarded as important for the following reasons A to C:

A: Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Visual acuity reduced (very common), vision blurred (common). *Comment: This functional loss is mainly considered to occur as a result of the underlying ocular disease. It may represent a symptom of an injection related event such as intraocular inflammation/infection or retinal tear/detachment. These complications pose important identified risk in the EU RMP.*
- Conjunctival haemorrhage (very common), conjunctival hyperaemia (common), ocular hyperaemia (common), vitreous haemorrhage (common), vitreous floaters (common), eye pain (very common), injection site pain (common), injection site, haemorrhage (common), injection site irritation (uncommon), lacrimation increased (common), foreign body sensation in eyes (common), abnormal sensation in eye (uncommon), eyelid irritation (uncommon). *Comment: These are local events likely caused by the intraocular injection procedure, -which are usually mild and fully reversible in nature. It is expected that HCPs are well familiar with these concomitant adverse effects of the IVT injection.*

B: Known risks that do not impact the risk-benefit profile (in relation to the severity of the indication treated):

- Detachment of retinal pigment epithelium (common), retinal degeneration (common), vitreous detachment (common), corneal erosion (common), corneal abrasion (common), punctate keratitis (common), corneal epithelium defect (uncommon).
  Comment: These events are likely procedure-related (however, "detachment of retinal pigment epithelium" and "retinal degeneration" could also be promoted by underlying disease) and may

result in longer-term complaints. However, no severe sequelae are expected, and these events are not assumed to impair the positive risk/benefit profile of Eyluxvi. It is expected that HCPs are well familiar with these potential adverse effects of the IVT injection.

C: Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication

- Blindness (rare).
  Comment: This event is rare and may also occur due to the underlying disease.

Reasons for considering other risks not important (including class effects)

Potential risk: Sustained intraocular pressure.

Issue: A persistent ocular hypertension (OHT) has been observed after intravitreal injection of VEGF inhibitors (ranibizumab, bevacizumab), leading to an assumed class effect of "sustained" IOP increase. The incidence of sustained OHT after intraocular administration of these VEGF inhibitors ranged between 3.1% and 11.9% in studies with 96 - 512 treated eyes. Two hypotheses have been described for the underlying mechanism of chronic OHT:

- The anti-VEGF antibodies (= high molecular proteins) may accumulate in the aqueous outflow channels including the trabecular meshwork or Schlemm's canal and obstruct aqueous outflow.
- Immunological reactions and low-grade inflammation post injection may be an additional mechanism leading to IOP elevations.

Both effects may be amplified by the quality of the injected VEGF inhibitor: aggregation of the antibody to higher molecular structures may enhance the obstruction of the outflow system. Also, contaminants such as silicone oil from the syringe barrel or rubber stopper may block the outflow system or induce subclinical inflammation (Bakri 2007 and 2009, Sniegowski 2010).

Comment: A transient increase of IOP, which is often observed after intravitreal injection of fluids, is considered an important identified risk of IVT aflibercept administration. It is attributed to an increase in vitreous volume (volume effect), which is compensated within 0.5 to 1 hours after injection, so that IOP normalises back to baseline values. Therefore, the volume effect is not responsible for a chronic elevation of IOP. Thorough monitoring of mean values over time for pre-injection IOP in the clinical Phase III trials with aflibercept indicated the there is no trend towards sustained IOP increase on treatment with aflibercept. Therefore, the assumed class effect of "sustained" IOP increase is not regarded as an important risk of treatment with aflibercept.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk: Endophthalmitis (likely infectious origin)

Risk-benefit impact: Endophthalmitis is an intraocular infection and may occur due to an infection with microorganisms, either through direct traumatic injury of the eye (exogenous infection) or through spreading of microorganisms from other areas of the body (endogenous infection). In cases of inflammation where no pathogens can be identified (no/negative culture growth of microorganisms observed), the condition may be characterised as "sterile endophthalmitis" or "non-infectious endophthalmitis".

Due to the risk of severe vision loss, treatment should be initiated as soon as possible, and, depending on cause and severity, may consist of topical and intravitreal application of antibiotics, corticosteroids, and surgical removal of matter and infected structures (drainage, vitrectomy).

The risk of endophthalmitis (and other intraocular infections) cannot be completely excluded but minimised through strict aseptic and sterile conditions when administering aflibercept. Only experienced and appropriately trained ophthalmologists should be charged with the injections, and patients should report any signs or symptoms of intraocular inflammation (e.g., visual acuity decreased, pain, photophobia, or redness) as soon as possible to introduce appropriate countermeasures in due time. Educational material is provided among other things to promote optimal administration technique.

The proportion of VEGF Trap-Eye exposed adult patients experiencing endophthalmitis in the study eye in the clinical studies was low (range from 0% to 0.9% in the VIEW 1 extension study); endophthalmitis is regarded as an uncommon ADR. Currently, the risk-benefit in terms of endophthalmitis is considered favourable for Eyluxvi.

Important Identified Risk: Intraocular inflammation

Risk-benefit impact:

Intraocular inflammations (other than endophthalmitis) are inflammations of defined structures of the inner eye (e.g., iritis, uveitis, iridocyclitis). Aside from endophthalmitis / intraocular inflammations with an infectious origin, there are also inflammations where no pathogens can be identified (either no culture performed or negative culture growth), the condition may be characterised as "sterile" inflammatory condition.

The cause of a sterile inflammation, independently of the administered drug, remains uncertain, and a multifactorial origin cannot be discarded. An intraocular inflammation generally constitutes a serious condition, which may lead to generalised eye inflammation and risk of blindness. Treatment should be initialised as soon as possible, and, depending on cause and severity, may consist of topical and intravitreal application of antibiotics, corticosteroids, and surgical removal of matter and infected structures (drainage, vitrectomy).

The risk of intraocular infections can be minimised through strict aseptic and sterile conditions when administering Eyluxvi (see endophthalmitis).

The proportion of adult patients exposed to VEGF Trap-Eye (aflibercept) who experienced intraocular inflammation (grouped term) in the study eye in the clinical studies ranged from 0% to 2.6% (VIEW 1 & 2 AMD studies). Single preferred terms events associated with intraocular inflammation are considered uncommon ADRs (e.g., iritis, uveitis, iridocyclitis) or rare ADRs (vitritis, hypopyon). Currently, the risk-benefit in terms of intraocular inflammation is considered favourable for Eyluxvi.

Important Identified Risk: Transient intraocular pressure increase

Risk-benefit impact: Chronically elevated intraocular pressure is a major risk factor for a condition called "glaucoma", which is characterised by a loss of nerve fibres in the optic nerve with the subsequent risk of blindness. However, many different factors may be responsible for the development of glaucoma, and increased intraocular pressure is not a mandatory prerequisite for the development of glaucoma (e.g., normal-tension glaucoma). Transient IOP increase following IVT injection is a well-known side effect of any IVT administration of liquids used for drug dissolution, but this condition is limited and usually resolved once the surplus fluid has been resorbed from the inner eye.

The proportion of adult patients exposed to VEGF Trap-Eye who experienced an increase in intraocular pressure (grouped term) in the study eye in the clinical studies ranged from 2.8% (VIVID-JAPAN DME study) to 13.6% (CRVO studies GALILEO & COPERNICUS), but the vast majority of these events were resolved. Systematic measurements of IOP during the clinical studies did not indicate a trend towards sustained IOP increase. "Intraocular pressure increased" (single preferred term) is considered a common ADR. Currently, the risk-benefit in terms of transient IOP increase is considered favourable for Eyluxvi.

Important Identified Risk: Retinal pigment epithelial (RPE) tears

Risk-benefit impact: The retinal pigment epithelium is the outer layer of the retina, and tears in that layer may occur secondary to AMD, following intravitreal injections, or for unknown reasons. These tears may be self-sealing or may require sealing by laser coagulation.

In clinical trials up to 1.9% of patients with underlying wet AMD who were treated with VEGF Trap-Eye developed RPE tear, while none of the patients treated for other aflibercept indications (CRVO, BRVO, myopic CNV, DME) had developed RPE tear. RPE tear is considered a common ADR. However, the total incidence of RPE tears with VEGF Trap-Eye in the AMD Phase III trials was in line with the known background incidences from literature; and the absence of RPE tear in the clinical studies investigating the non-AMD indications of aflibercept suggests that RPE tear development caused by IVT treatment with aflibercept is rather unlikely. Currently, the risk-benefit in terms of RPE tear is considered favourable for Eyluxvi.

Important Identified Risk: Cataract (especially of traumatic origin)

Risk-benefit impact: Cataract (clouding of lens) may occur spontaneously (particularly in the elderly), as a side effect of certain drugs, or following outside influences such as irradiation or mechanical injury (traumatic cataract).

Thus, the needle injury required to inject Eyluxvi through the lens into the eyeball could cause such a traumatic cataract. However, by correct IVT procedure and a correct angle of the needle while injecting, the risk of cataract development can be minimised.

The proportion of patients exposed to VEGF Trap-Eye who experienced traumatic cataract in the study eye in the clinical studies ranged from 0% to 2.8% (VIVID-DME & VISTA-DME). Various forms of cataract (cortical, nuclear, subcapsular) are considered common ADRs; traumatic cataract is regarded as a rare ADR.

There is currently no evidence that the occurrence of a traumatic cataract is increased on treatment with aflibercept. However, as this might be a hypothetical result of the lens perforation, it has been included as important identified risk. Currently, the risk-benefit in terms of cataract development is considered favourable for Eyluxvi.

Important Potential Risk: Medication error

Risk-benefit impact: There is an excess volume in the marketed vial which exceeds the recommended net dose of 2 mg aflibercept per injection. Thus, injection of more than the approved volume results 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.

Important Potential Risk: Off-label use and misuse

Risk-benefit impact: As with other drugs, aflibercept might be intentionally used other than recommended, or in clinical conditions outside the approved indications. Aflibercept does not have any dependence potential. Since the clinical experience with aflibercept in such off-label use is limited, any case of off-label use is currently considered an important potential risk.

In addition, intentional off-label use in the context of multiple use of single use product (vial splitting) has been observed with aflibercept reference product. The Eyluxvi vial is approved for single eye use only.

Important Potential Risk: Embryo-fetotoxicity

Risk-benefit impact: As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following systemic administration of anti-VEGF therapies might result in adverse effects on pregnancy. The current experience with IVT-administered anti-VEGF therapies in pregnancy is sparse (single cases reported only) and thus inconclusive. However, early loss of pregnancy after IVT bevacizumab injection has been reported in a very few instances (Georgalas 2012). Therefore, particular attention is paid to that safety issue. No cases of embryo-fetotoxicity were reported during the clinical development programme; however, pregnant females were excluded from clinical study participation. Current post-marketing surveillance data of aflibercept do not suggest an increased risk of embryo-fetotoxicity on treatment with Eyluxvi.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable since this is the first submission of a RMP for Eyluxvi.

SVII.3 Details of important identified risks, important potential risks, and missing information

Overview of data sources (clinical studies and post-marketing data)

Overview of clinical studies

Important identified and potential risks were determined considering the safety data of aflibercept 40mg/mL reference product (Eylea, named VEGF Trap-Eye (VTE)) and of the biosimilar Eyluxvi in the following studies:

Studies in wet AMD

- Pooled data of the pivotal Phase III AMD randomised controlled studies VIEW 1 and VIEW 2 (Schmidt-Erfurth 2014)
- Open-label VIEW 1 extension study (VGFT-OD-0910, Kaiser 2017)
- Phase III AMD randomised controlled study SIGHT (Li 2017)
- Phase IV AMD study ALTAIR (Ohji 2020)
- Phase I clinical study (ALT-L9-01)
- Phase III ALTERA study (ALT-L9-03)

CRVO studies

- Pooled data of the Phase III CRVO randomised controlled studies GALILEO and COPERNICUS (Pielen 2017)

BRVO study

- Phase III BRVO randomised controlled study VIBRANT (Clark 2016)

Myopic CNV study

- Phase III myopic CNV randomised controlled study MYRROR (Ikuno 2015)

DME studies

- Pooled data of the pivotal Phase III DME randomised controlled studies VIVID-DME and VISTA-DME (Heier 2016)
- Randomised, controlled Phase III DME study VIVID-EAST (Chen 2020)

- Single-arm, open-label study Phase III DME study VIVID-JAPAN (Terasaki 2019)

ROP study

- Randomised, open-label, two-arm, controlled Phase III ROP study FIREFLEYE (24 weeks) and its extension study FIREFLEYE NEXT (Stahl 2024)

The study designs are outlined below.

Studies in wet AMD

For AMD, pooled data (**VIEW 1 [VGFT-OD-0605]** and **VIEW 2 [SN 91689]** studies) from baseline through 96 weeks are primarily presented. In Year 1 of the studies, patients received fixed-dose treatment with ranibizumab 0.5 mg every 4 weeks (RQ4), VEGF Trap-Eye (VTE) 0.5 mg every 4 weeks (0.5Q4), VEGF Trap-Eye (VTE) 2 mg every 4 weeks (2Q4), and VEGF Trap-Eye 2 mg every 8 weeks (2Q8). The original dose of Year 1 (i.e., 0.5 or 2.0 mg per injection) was maintained in Year 2 of the studies, but the treatment intervals could be extended to 12 weeks at maximum according to pre-specified re-treatment criteria (modified quarterly dosing). The safety data of the 1,824 SAF patients treated in VIEW1 and VIEW 2 are presented by randomised treatment group at Baseline, i.e., RQ4 (N=595), VTE 0.5Q4 (N=601), VTE 2Q4 (N=613), and VTE 2Q8 (N=610).

VIEW 1 patients of any randomised treatment group who had completed the 96 weeks of the core study had the opportunity to start or continue treatment with VEGF Trap-Eye 2 mg in the open- label, multi-dose VIEW 1 extension study (VGFT-OD-0910) conducted for assessing the long-term safety and tolerability of aflibercept. During the study, patients were randomised in a 1:1:1 ratio to 3 treatment groups which differed in the packaging or sterilization techniques of VEGF Trap-Eye 2 mg (i.e., vials, or one of the externally sterilised prefilled syringes [ethylene oxide, ETO, or hydrogen peroxide, VHP]) in order to investigate the safety profile of the different product configurations and external sterilization techniques. VEGF Trap-Eye 2 mg was to be administered no more frequently than every 4 weeks and no less frequently than every 12 weeks (later amended in the US to 8 weeks). A total of 323 VIEW 1 completers were enrolled in VGFT-OD-0910, 320 received study drug treatment in the extension phase with VEGF Trap-Eye in the study eye (69 from the original RQ4 group, 87 from the original 0.5Q4 group, and 92 and 72 from the original 2Q4 and 2Q8 groups, respectively), and 281 were randomised to the different product specifications (93 to vials, 94 to ETO, and 94 to VHP). Three of the 323 subjects enrolled in the VIEW 1 extension study were last treated with VEGF Trap-Eye 2 mg at Week 96 of the core VIEW 1 study (all 3 were randomised in the 2Q4 group) but did not receive treatment in the extension phase. These patients were nevertheless included in the safety set of the VIEW 1 extension study, as they had received VEGF Trap-Eye at Week 96 of the VIEW 1 core study and thus were exposed to VEGF Trap-Eye.

The mean treatment duration in VGFT-OD-0910 (excluding the core study period of 96 weeks) for all enrolled extension study patients (N=323) was 110.4 weeks. The safety data presented in this module is based on the safety events occurring during the extension period in the 323 patients (SAF) who were exposed to VEGF Trap-Eye in the extension period (referred to as " VEGF Trap-Eye total group"). Two additional analysis groups were defined, with i) patients who had been treated with ranibizumab in the preceding core study period (N=69) and ii) patients who had been treated with VEGF Trap-Eye at any dose (i.e., 0.5Q4, 2Q4, or 2Q8) already during the core study period (N=254).

This separation was deemed reasonable, because only the 254 patients from the original VEGF Trap-Eye groups were on true long-term treatment with VEGF Trap-Eye (i.e., beyond 96 weeks of treatment, for up to approximately 5 years in total). In the 320 subjects who also received treatment in the study extension period, a total of 7,215 injections were administered in the study eye from the original baseline in VIEW 1 through the end of the extension period (range: 12 to 61 injections), and the overall mean treatment duration was 48.9 ± 9.8 months (range: 23 to 64 months).

SIGHT (SN 13406) was a randomised, double-masked, photodynamic therapy-controlled Phase III study evaluating the efficacy, safety, and tolerability of VEGF Trap-Eye in Chinese subjects with wet AMD. A total of 304 patients were randomised in a 3:1 ratio to treatment with VEGF Trap-Eye 2 mg (N=228) or control treatment with PDT (N=76). Primary efficacy assessments were performed at Week 28. Patients in the VEGF Trap-Eye 2 mg group received the first 3 IVT injections with VEGF Trap-Eye every 4 weeks (i.e., at Baseline, Week 4 and Week 8) and subsequently every 8 weeks until Week 48 (i.e., at Weeks 16, 24, 32, 40, and 48). At Weeks 28 and 36, sham injections were additionally required. Patients in the PDT control group received one PDT procedure at baseline and were allowed to undergo additional PDT procedures through Week 28 as indicated according to local clinical practice and the clinical judgment of the investigator. Sham injections were administered for maintaining the blind (while patients in the VEGF Trap-Eye group underwent a sham PDT procedure at baseline and additional sham PDT procedures as indicated according to local clinical practice and the clinical judgment of the investigator). At Week 28, after all variables for the primary efficacy endpoint had been assessed and the data recorded, subjects in the PDT group were to receive one injection with VEGF Trap-Eye 2 mg and subsequent injections with VEGF Trap-Eye 2 mg at Weeks 32, 36, 40, and 48. Actually, 71 out of the 76 patients randomised to the PDT control group were exposed to VEGF Trap-Eye. Safety data are presented for the entire study period through Week 52 by randomised treatment group (N=76 and 288, respectively) and additionally in the VEGF Trap-Eye total group that includes all study patients who were exposed to VEGF Trap-Eye (N=299; only AEs occurring during or after the first VEGF Trap-Eye exposure are counted in the 71 original PDT patients who received VEGF Trap-Eye from Week 28 onwards).

ALTAIR (SN17668) was a randomised, open-label phase 4 study evaluating the efficacy and safety of repeated doses of intravitreal aflibercept with variable treatment intervals in Japanese subjects with neovascular age-related macular degeneration. Eligible subjects received an IVT injection of aflibercept at every scheduled treatment visit. After completion of treatment at Week 16, the timing of the subsequent treatment visits was determined at the previous treatment visit by the treating physician based on the criteria of the Treat and Extend regimen. Subjects who had completed the run-in phase were randomly assigned to one of the two treatment arms of the study (2-week [2W] adjustment group or 4-week [4W] adjustment group) in 1:1 ratio at Week 16. A total of 247 patients were randomised, 7 patients were treated but not randomised.

2W adjustment group (N=124): Aflibercept IVT injection at Week 0, Week 4, Week 8 and Week 16, followed by the variable treatment intervals based on the criteria of the Treat and Extend regimen.

If the study eye of a subject met the respective criteria for shortening or extension, length of either extension or shortening of the treatment interval was 2 weeks from the last interval, respectively.

4W adjustment group (N=123): Aflibercept IVT injection at Week 0, Week 4, Week 8 and Week 16, followed by the variable treatment intervals based on the criteria of the Treat and Extend regimen.

Shortening of interval: If the study eye of a subject met the criteria for shortening the treatment interval was shortened by 2 weeks. However, if the last treatment interval of a subject had been extended by 4 weeks from the second last interval, the treatment interval was shortened by 4 weeks.

Extension: If the study eye of a subject met the criteria for extension, length of extension of the treatment interval was 4 weeks. However, when a subject had a history of receiving treatment with interval shortened by 4 weeks during this study, the length of the extension was 2 weeks.

Subjects were evaluated at Week 52 and Week 96, regardless of treatment schedule. In study eyes, only the study drug was administered while fellow eyes could receive any domestically approved treatments. If a subject was judged to need any extra treatment in the study eye either using study drug or non-

study treatment, the subject terminated the study. Ophthalmic evaluations were done at every treatment and evaluation visits other than visit for safety follow-up using visual acuity test with ETDRS score, slit lamp and indirect ophthalmoscopy, and optical coherence tomography (OCT). Fundus photography (FP), FA and indocyanine green angiography (ICGA) were conducted at visit for screening, Week 52 and Week 96. In addition to these ophthalmic evaluations, general evaluation and vital sign assessment in subjects were used for safety evaluation methods. Aflibercept was administered every 4 weeks until Week 8 (Run-in phase). Subjects who completed the Run-in phase were randomly assigned to one of the two treatment arms of the study (2W adjustment group or 4W adjustment group) in 1:1 ratio at Week 16. After the IVT injection at Week 16, treatment was followed by a Treat and Extend regimen with variable treatment intervals up to Week 96 (treatment phase). During Week 16 to Week 96, treatment interval between two injections must not be less than 8 weeks and must not be more than 16 weeks.

ALT-L9-01: The primary objective of the Phase I, first in human study of Eyluxvi in subjects with wet AMD was to evaluate the safety, efficacy and pharmacokinetics of ALT-L9 in patients with neovascular (wet) AMD. To be eligible for this study, patients were to have received prior anti VEGF treatment for wet AMD in the study eye, but at least 8 weeks prior to the baseline visit. Both Eyluxvi and Eylea were given at dose regimen of 3 doses every 4 weeks, for a total of 8 weeks. A total of 28 patients were randomised (14 per group), completed study treatment and received all treatment doses.

ALT-L9-03 (ALTERA): This randomised, Phase III, double masked, parallel group, multicentre study compared the efficacy, safety, pharmacokinetics and immunogenicity of Eyluxvi to Eylea in wet AMD patients. 216 patients were treated with Eyluxvi and 215 patients were treated with Eylea. Both drugs Eyluxvi and Eylea given at dose regimen of q4w at baseline, Week 4, and Week 8 and thereafter q8w at Weeks 16, 24, 32, 40, and 48 weeks.

CRVO studies

In the Phase III CRVO study **COPERNICUS** (VGFT-OD-0819), patients received either VEGF Trap-Eye or sham (2Q4) in the first 6 months (Week 24); in the second 6 months sham patients were able to receive active treatment depending on re-treatment criteria defined in the protocol. All subjects were allowed to continue PRN treatment through Year 2 (Week 100).

In the Phase III CRVO study **GALILEO** (SN 14130), patients were treated either with VEGF Trap-Eye or sham up to 52 weeks. During the 52 weeks study duration, sham patients were not foreseen to be treated with VEGF Trap-Eye but could be treated with VEGF Trap-Eye from Week 52 to Week 76.

The pooled safety data of the 2 CRVO studies are shown for the entire study period from Baseline to Week 76/100 (the study period was 76 weeks in GALILEO and 100 weeks in COPERNICUS). Treatment groups for data presentation are based on original randomisation, i.e., 142 patients randomised to sham with subsequent PRN treatment and 218 patients randomised to VEGF Trap-Eye 2Q4 with subsequent PRN treatment. In addition, AEs in all patients from either randomisation group who received at least one active injection with VEGF Trap-Eye are summarised from the day when the first injection was administered (N=317; i.e., excluding the 43 patients of the sham-PRN group who never received VEGF Trap-Eye, referred to as "VEGF Trap-Eye total group").

BRVO study

VIBRANT (VGFTe RVO-1027) was a randomised, double-masked, active controlled 52- week study to evaluate the efficacy, safety, and tolerability of repeated IVT administration of VEGF Trap-Eye compared with grid laser photocoagulation in subjects with macular oedema secondary to BRVO. A total of 183 patients were randomised and exposed to study treatment (91 in the VEGF Trap-Eye group and 92 in the laser group). The study was conducted by Regeneron Pharmaceuticals, Inc. in North America (USA, Canada) and Japan. Patients in the VEGF Trap-Eye group received VEGF Trap-Eye 2Q4 through (including) Week 24, then 2Q8 through Week 48. Sham IVT injections were administered every 8 weeks starting from Week 28, alternating with VEGF Trap-Eye injections every 8 weeks, through Week 44. The last active injection with VEGF Trap-Eye was on Week 48. Patients in the VEGF Trap-Eye group also received one sham laser treatment on Day 1. Rescue treatment with active laser in this group was possible, if patients had met the pre- defined criteria at Week 36. Patients randomised to the laser group received grid laser photocoagulation treatment at Day 1, and sham IVT injections every 4 weeks from Day 1 through Week 48. Rescue treatment with laser was possible from Week 12 onwards (minimum intervals of 12 weeks from previous laser treatment) in those patients who had met the pre-specified criteria. Patients in the laser arm could become eligible for rescue treatment with VEGF Trap-Eye beginning at Week 24. In this case, they were to receive 3 initial VEGF Trap-Eye 2 mg injections every 4 weeks, followed by injections every 8 weeks. Safety data are presented in this RMP version for the final Week 52 study data as per randomised treatment group, i.e., based on the 91 patients in the VTE 2 mg group and the 92 patients in the Laser + VTE 2 mg group (i.e., patients randomised to initial treatment with laser through Week 20 and the option for VEGF Trap-Eye rescue therapy beginning at Week 24). In addition, the VEGF Trap-Eye total group (N=158) includes all patients who had received VEGF Trap-Eye at least once (i.e., in addition to patients from the VEGF Trap-Eye treatment group, the 67 patients in the Laser + VTE 2 mg group who had received rescue treatment with VEGF Trap-Eye beginning at Week 24). In this group, all adverse events occurring after the first VEGF Trap-Eye injection are counted.

Myopic CNV study

In the multicentre, randomised, double-masked, sham-controlled, Phase III myopic CNV study **MYRROR** (SN 5170), a total of 122 Asian subjects with active subfoveal or juxtafoveal CNV secondary to pathologic myopia were randomised to receive either VEGF Trap-Eye 2.0 mg or sham injection. The primary efficacy endpoint (mean change in BCVA) was evaluated after 24 weeks of treatment (injections from baseline through Week 20). In this study period, subjects in the VEGF Trap-Eye group (N=91) received an active injection at Baseline and were then assessed at regular intervals of 4 weeks for the need of a repeated injection based on pre- defined re-treatment criteria (i.e., in case of recurring or persisting CNV). If no active injection was required, these subjects received a sham-injection. In the sham group (N=31), subjects underwent the same study-related procedures, but were solely treated with sham injections.

After the primary endpoint assessment at Week 24, all patients randomised to sham who continued the study (N=25) received one mandatory injection with active VEGF Trap-Eye and continued treatment in the same way as in the VEGF Trap-Eye 2 mg group, i.e., active injections, when pre- specified re-treatment criteria were met, or a sham injection otherwise. Patients were still monitored at monthly intervals; the last active injection could be given at Week 44, and the final study assessments were performed at Week 48.

Safety results of the MYRROR were published for treatment groups as randomised (i.e., Sham + VEGF Trap-Eye 2 mg group [N=31] vs. VEGF Trap-Eye 2 mg group [N=91]) and for all patients who were treated with active VEGF Trap-Eye at least once during the study period (VEGF Trap-Eye total group [N=116]).

DME studies

VIVID-DME (SN 91745) and **VISTA-DME** (VGFT-OD-1009) were both 3 year, randomised, double-masked, active-controlled, multicentre, Phase III studies of the efficacy and safety of repeated doses of VEGF Trap-Eye in subjects with DME with central involvement. In VIVID-DME, a total of 404 subjects (SAF) were treated in European countries, Australia, and Japan. In VISTA-DME, a total of 461 subjects (SAF) were treated in the US. The studies had nearly identical overall study designs and are described together unless otherwise indicated.

Patients were randomised to 1 of the following 3 treatment groups: VEGF Trap-Eye 2Q4 to Week 148, VEGF Trap-Eye 2Q8 (after 5 initial monthly doses), with sham injections at alternating visits, to Week 148, or laser photocoagulation through Week 148 plus sham injection. Subjects in the VEGF Trap-Eye groups received sham laser at Baseline and at visits, at which subjects met the criteria for laser re-treatment (no more often than every 12 weeks). The last administration of study treatment in all treatment groups was at Week 144.

Subjects in all groups were assessed for additional treatment (i.e., "rescue" treatment with VEGF Trap-Eye for the laser subjects, and laser for the VEGF Trap-Eye subjects) for inadequate responders at each visit starting at Week 24. Additional treatment was to be administered if pre-specified criteria were met.

During Year 3, subjects randomised to the laser group who did not meet the criteria for additional treatment previously could receive VEGF Trap-Eye as needed (PRN) according to re-treatment criteria from Week 100 through the end of the study (Week 144).

Fellow eye treatment for DME with anti-VEGF agents was allowed in both studies. In VIVID-DME, standard of care was used (including ranibizumab or bevacizumab; licensed treatment preferred). In VISTA-DME, VEGF Trap-Eye was provided and required as fellow eye treatment (although ranibizumab could be used, if VEGF Trap-Eye was unavailable due to logistical reasons).

The primary efficacy endpoint in both studies was the change in ETDRS letter score from Baseline to Week 52.

The study design of **VIVID-EAST** (SN 15161) was very similar to the designs of the pivotal studies VIVID-DME and VISTA-DME in the first year, and was conducted in China, Hong Kong, Republic of Korea, and the Russian Federation. The primary efficacy variable was the change from baseline in BCVA in ETDRS letter score at week 52. A total of 378 SAF patients were randomised to treatment with laser photocoagulation (N=124), the VEGF Trap-Eye 2Q4 (N=127), or VEGF Trap-Eye 2Q8 (N=127). Laser patients were treated with laser photocoagulation at baseline and from week 12 onwards, if laser-re-treatment criteria were met. Patients in the VEGF Trap-Eye 2Q4 group received VEGF Trap-Eye 2 mg at monthly intervals continuously through Week 48, and patients in the VEGF Trap-Eye 2Q8 group received VEGF Trap-Eye 2 mg every 2 months following 5 initial injections at monthly intervals (i.e., from Baseline to including Week 16) through Week 48. As with the pivotal studies, additional treatment with VEGF Trap-Eye in the laser group (or with laser in the VEGF Trap-Eye groups) was permitted from Week 24 onwards in the case that pre-defined additional treatment criteria were met. The last study treatment was administered on Week 48; final study assessments were performed at Week 52. The safety data are presented by randomised treatment group, and in the VEGF Trap-Eye total group considering all TEAEs that occurred at or after the first administration of VEGF Trap-Eye (N=299; i.e., the 254 patients initially randomised to VEGF Trap-Eye treatment plus 45 laser group patients who received VEGF Trap-Eye as additional treatment during the study at Week 24 at the earliest). Generally, the considerations about the interpretation of the safety data in the pivotal DME studies do also apply to VIVID-EAST.

VIVID-JAPAN (SN 15657) was a 1-year, open-label Phase III study performed in Japan with a treatment schedule that was generally similar to the 2Q8 arm in the randomised, controlled studies, i.e., all subjects were treated (in an open-label fashion) with VEGF Trap-Eye 2 mg every 2 months

(2Q8) after 5 initial doses at monthly intervals (i.e., 2Q4 up to Week 16). Last treatment was on Week 48; the final endpoint assessments were performed at Week 52. No additional treatment of the study eye with laser was permitted. Fellow eye treatment was allowed as per local standard of care/medical routine. Study assessments included effectiveness and safety of treatment as well as PK analyses. The safety analyses were performed without further stratification in a total of 72 subjects (one of the 73 enrolled and treated patient was excluded from the SAF because he/she withdrew consent).

ROP studies

FIREFLEYE (SN 20090) was a Phase III, multi-centre, open-label, randomised, two arm, controlled study to assess the efficacy, safety, and tolerability of IVT aflibercept compared to laser photocoagulation in preterm infants with ROP. The study consisted of a screening phase followed by a baseline visit when subjects were randomised either to aflibercept or laser (ratio: 2:1), followed by a 23-week treatment period, which equals a 24 week total study duration. One or both eyes were treated based on the study eligibility criteria as assessed by the investigator. Subjects were also allowed to be retreated or administered rescue treatment (laser for the aflibercept arm; aflibercept for the laser arm). The primary efficacy endpoint was the proportion of subjects with absence of active ROP and unfavourable structural outcomes at 24 weeks after starting study treatment based on investigator's assessment. Key secondary efficacy endpoints addressing the primary objective were subjects with requirement for intervention with a second treatment from baseline to Week 24 and subjects with recurrence of ROP from baseline to Week 24, which were also analysed using a similar Bayesian statistical model as for the primary endpoint. A total of 118 subjects were randomised, 75 to aflibercept and 38 to the laser arm. This RMP version includes the final FIREFLEYE study results through Week 24. Safety results of the FIREFLEYE study are presented for treatment groups as randomised (i.e., VEGF Trap-Eye 0.4 mg group [N=75] vs. Laser group [N=38]) and additionally for all patients who were treated with VEGF Trap-Eye at least once during the study period (VEGF Trap-Eye total group [N=79; i.e., the 75 patients initially randomised to VEGF Trap-Eye treatment plus 4 laser group patients who received VEGF Trap-Eye as rescue treatment during the f the study].

FIREFLEYE NEXT (SN 20275) is a Phase IIIb study which follows up on ocular, neurodevelopmental and overall clinical outcomes until 5 years of age. All patients treated in the FIREFLEYE study were offered participation.

Post-marketing data

In addition to the clinical study data, the post-marketing cases for the important identified and potential risks, cumulating from market launch of Eylea through to cut-off date 15 SEP 2017 is available (Pospisil 2024), are provided. These cases include spontaneously reported cases and cases from non-interventional studies (incl. solicited sources such patient support programmes and market research programmes), both medically confirmed and non-confirmed cases, and both valid and invalid cases (i.e., one case might include more than one patient).

Important Identified Risk: Endophthalmitis (likely infectious origin)

Potential mechanisms:

Despite meticulous sterile technique, there is always a risk of introducing microorganisms into the vitreous cavity during the intravitreal injection procedure. Even low levels of bacteria or fungi can potentially cause infection if introduced into the eye. Source of pathogenic agents is in most cases the patient's conjunctival bacterial flora.

Evidence sources and strength of evidence:

Data from clinical trials, post-marketing surveillance and literature.

Inflammation of the inner structures of the eye (in particular the vitreous body, which fills the globe) may occur as a result of an infection with microorganisms, either through direct traumatic injury of the eye (exogenous infection) or through spreading of microorganisms from other areas of the body (endogenous infection). This pathogen-caused inner eye (intraocular) infection is called endophthalmitis. In cases of inflammation where no pathogens can be identified (no/negative culture growth of microorganisms observed), the condition may be characterised as "sterile endophthalmitis" or "non-infectious endophthalmitis".

Characterisation of the risk:

Culture positive and culture negative endophthalmitis is an uncommon to rare adverse event.

Post-injection, sterile intraocular inflammation is an uncommon to rare adverse event.

Frequency

AMD - Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks): The overall 96-week incidence of endophthalmitis (likely infectious origin, hereinafter referred to simply as endophthalmitis) was 0.3% and 1.0% in the combined VEGF Trap-Eye and in the ranibizumab group, respectively. The incidence of endophthalmitis in the VEGF Trap-Eye treatment arms was very low (0.3%), which is below the incidence reported in the literature for IVT administration of VEGF inhibitors (1.0% to 1.1%; see background incidence/prevalence information).

AMD - VIEW 1 long-term extension study: Three patients (one in the former randomised ranibizumab group [1.4%] and 2 in the former randomised VEGF Trap-Eye groups [0.8%] experienced endophthalmitis in the study eye during the extension study period. There were no meaningful differences compared with the frequency of endophthalmitis reported from the pivotal AMD trials through Week 96.

AMD - Clinical Trial SIGHT (52 weeks): No events pertaining to the group of endophthalmitis in the study eye were reported during the course of the SIGHT study.

AMD - Clinical Trial ALTAIR (52 weeks): No events pertaining to the group of endophthalmitis in the study eye were reported during the course of the ALTAIR study.

AMD - Clinical Trial ALTERA (48 weeks): The overall 48-week incidence of endophthalmitis was 0.5% in the Eyluxvi group and 0.9% in the Eylea group.

CRVO Clinical Trials COPERNICUS and GALILEO (pooled data. 76/100 weeks): One case of endoph-thalmitis (0.3% of VEGF Trap-Eye-treated patients) in the study eye was reported from the pooled CRVO studies. No endophthalmitis events were reported during sham treatment.

BRVO Clinical Trial VIBRANT (52 weeks): No cases of endophthalmitis in the study eye were reported through Week 52 in the BRVO study VIBRANT.

Myopic CNV Clinical Trial MYRROR (48 weeks): No cases of endophthalmitis were reported in the MYRROR study through Week 48.

DME - Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data. 148 weeks'): Three cases of endophthalmitis were reported through Week 148 (2 patients in the 2Q4 group and one patient in the 2Q8 group.

DME - Clinical Trial VIVID-EAST (52 weeks): No events pertaining to the group of endophthalmitis in the study eye were reported in the VIVID-EAST study.

DME - Open-label Clinical Trial VIVID-JAPAN (52 weeks): No cases of endophthalmitis in the study eye were reported in the VIVID-JAPAN study.

ROP - Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data): No events pertaining to the group of endophthalmitis in the VEGF Trap-Eye-exposed eye were reported in the FIREFLEYE or the FIREFLEYE NEXT study.

Post-Marketing Data of Eylea

Considering the sales figures and the estimated cumulative patient exposure in the post-marketing period of Eylea until 30 SEP 2017, the reporting rate of endophthalmitis cases (N=844) was 0.05 cases per 1,000 sold vials (0.005%) and 0.36 cases per 1,000 patient years (0.036%). This incidence reported during post-authorisation use is within the reported incidence reported in the clinical development programme of Eylea and in the literature with the IVT injection of anti-VEGF agents and other drugs (Pospisil 2024).

Information on seriousness and outcome

Information on seriousness and outcome is scarce, especially in post marketing data: Even though patients may recover without sequelae, endophthalmitis may cause severe vision loss or even blindness.

Background incidence/prevalence

Incidence of endophthalmitis after IVT anti-VEGF injections

A systematic review of 278 publications was published in 2011 to identify adverse events associated with anti-VEGF injections. Endophthalmitis was reported with incidence rates below or equal to 0.04 (95% CI: 0.02-0.08), 0.05 (95% CI: 0.03-0.10) per 100 injections for ranibizumab and bevacizumab, respectively (van der Reis 2011). Another systematic review identified 5 controlled trials that evaluated the efficacy or safety of administration of anti-VEGF agents compared with conventional therapy in 383 preterm infants with ROP; no cases of endophthalmitis were reported (Sankar 2018).

Reports from wet AMD studies

The Phase III trials for ranibizumab (Lucentis) - ranibizumab for wet AMD (MARINA) and ranibizumab versus verteporfin for wet AMD (ANCHOR) - demonstrated a low rate of endophthalmitis. At 96 sites in the US, of the 716 patients enrolled in the 2-year MARINA study, 478 patients received 0.3 mg or 0.5 mg ranibizumab and 238 patients received sham injection. The endophthalmitis rate was 1.0% (5 of 477 patients), or, alternatively, a rate per injection of 0.05% (5 of 10,443 total injections). Similar incidence rates of 1.1% (3 of 277 patients or of 0.05% per injection (3 of 5,921) were reported in the ANCHOR study where 5,921 injections of ranibizumab were administered. In this study 423 patients were randomised 1:1:1 in 83 international sites to verteporfin photodynamic therapy (PDT) plus monthly sham intraocular injection (n=143) or to sham verteporfin PDT plus monthly IVT ranibizumab (0.3 mg or 0.5 mg) injection (140 each in the 2 ranibizumab groups). A review of safety data of 3,252 patients with over 28,500 IVT ranibizumab injections in the ANCHOR, MARINA, PIER, and SAILOR studies reported an endophthalmitis incidence of 0.05% per injection (Mitchell 2010).

In the United Kingdom (UK) a 12-month prospective, double masked, multicentre, randomised controlled trial (ABC Trial) enrolled 131 patients (mean age 81) from 3 centres with wet AMD to receive IVT bevacizumab (1.25 mg, 3 loading injections at 6-week intervals followed by further treatment if required at 6-week intervals, n=65) or the standard treatment available at the start of the trial (PDT with verteporfin for predominantly classic type wet AMD, n=16, or IVT pegaptanib, n=38, or sham treatment, n=12, for occult or minimally classic type AMD). There were no cases of endophthalmitis (Tufail 2010).

In 2 Phase III multicentre trials (VISION I and II trial), which evaluated 2 years of therapy with pegaptanib sodium injection for wet AMD, a total of 7,545 IVT pegaptanib sodium injections and 2,557 sham injections were administered. A total of 1,190 patients were randomised to receive 0.3 mg, 1 mg, or 3 mg of pegaptanib sodium by intravitreous injection or sham injection every 6 weeks. The reported endophthalmitis incidence per injection was 0.16%. Most of the cases (75%) resulted from violations of the injection preparation protocol and the rate dropped to 0.07% in the 2nd year after reinforced aseptic procedure. During the 3rd year of the VISION trials 422 patients received 3,227 pegaptanib injections and the endophthalmitis rate per injection was 0.06%.

No cases of endophthalmitis or intraocular inflammation were reported in the randomised controlled wet AMD-PCV studies LAPTOP (Oishi 2013) or EVEREST (Lim 2020).

Reports from CRVO studies

A Phase III, prospective, randomised, sham controlled, double masked, multicentre clinical trial of ranibizumab injection in patients with macular oedema secondary to CRVO (CRUISE Study) enrolled 392 patients to monthly IVT injections of 0.3 mg or 0.5 mg of ranibizumab (n=262) or sham (n=130) injections and reported no events of endophthalmitis (Brown 2010, Campochiaro 2011).

A dose-ranging, double-masked, multicentre, sham controlled, Phase II trial included 98 subjects with CRVO of <6 months duration and assigned them (1:1:1) to receive pegaptanib sodium (0.3 mg and 1 mg, n=33 each) or sham (n=32) injections every 6 weeks for 24 weeks. This study was conducted in practitioners' offices and clinics in Australia, France, Germany, Israel, Spain, and the US. No subject developed endophthalmitis (Wroblewski 2009).

Reports from BRVO studies

The Pan American Collaborative Retina Study Group conducted an interventional, retrospective, comparative multicentre study with 63 patients (63 eyes) with macular oedema secondary to BRVO that were treated primarily with IVT bevacizumab. Patients were recruited at 8 institutions in Costa Rica, Venezuela, Puerto Rico, Brazil, Peru, Mexico, Argentina, and Spain and had at least 24 months of follow-up. During the 24 months, there were 138 injections recorded in the 1.25 mg dose group and 109 injections in the 2.5 mg dose group. There were no cases of endophthalmitis (Wu 2010).

In a randomised controlled trial of intravitreal 0.5-ranibizumab injection versus standard grid lase for macular oedema following BRVO, there were no events of endophthalmitis, during the 12-month-long treatment period. A total of 36 patients with vision loss in one eye attributable to macular oedema were included in the study (Tan 2014).

In a randomised controlled clinical trial (BRAVO) to the assess 12-month efficacy and safety of intraocular injections of 0.3 mg (n=134) or 0.5 mg ranibizumab (n=131) vs. sham treatment (n=132) in patients with macular oedema secondary to BRVO (n=397), one case of endophthalmitis was reported in the ranibizumab 0.5 mg treatment group (n=131, incidence 0.8%) (Campochiaro 2010). The follow-up study (HORIZON) on ranibizumab for macular oedema due to RVO reported no cases of endophthalmitis (in BRVO or CRVO) during the 12 months follow-up period (Heier 2012).

The SCORE-BRVO study compared the efficacy and safety of 1 mg and 4 mg doses of intravitreal triamcinolone with standard of care (grid photocoagulation in eyes without dense macular haemorrhage and deferral of photocoagulation until haemorrhage cleared in eyes with dense macular haemorrhage) for eyes with vision loss associated with macular oedema secondary to BRVO. A total of 411 participants were randomised and followed for 12 months. Through month 12, there were neither reports of infectious endophthalmitis in the standard of care group (n=137) nor in the 1 mg triamcinolone group (n=136),

but one case (incidence=0.7%) was reported in the 4 mg triamcinolone group (n=138) 3 days after the third injection (Scott 2009).

Russo (2009) compared bevacizumab with macular laser grid photocoagulation in a randomised, controlled study in 30 consecutive eyes with macular oedema in BRVO) and did not report any no case of endophthalmitis.

Parodi (2006) compared the effectiveness of sub-threshold grid laser treatment (SGLT) with infrared micropulse diode laser alone (n=13) or in combination with intravitreal triamcinolone injection (n=11) in BRVO patients and did not observe any endophthalmitis event during the 12 months follow-up study period.

Donati (2012) evaluated the long-term efficacy of intravitreal bevacizumab (IVB) versus combined IVB and macular grid laser photocoagulation for the treatment of macular oedema secondary to BRVO in an open-label study and did not observe any no sterile nor infectious endophthalmitis event.

Reports from myopic CNV studies

In a case series, records of 35 consecutive patients who were treated with intravitreal injection of bevacizumab from 18 DEC 2008, through 20 JAN 2009 were reviewed. Of the 35 patients, five developed severe intraocular inflammation. There were three patients with myopic CNV. All five cases were culture negative (Sato 2010).

In a Japanese study, bevacizumab was aliquoted into smaller doses (5 mg/0.2 ml x 20). Intravitreal bevacizumab (1.25 mg/0.05 ml) was injected into nineteen eyes of fifteen patients, two of whom (three eyes) had myopic CNV. Ocular inflammation occurred in 14 eyes of 11 patients, including both of the myopic CNV patients. Both myopic CNV patients required pars planta vitrectomy (Yamashiro 2010).

No cases of endophthalmitis were reported in the myopic CNV study RADIANCE with 277 patients (Wolf 2014).

Reports from DME studies

A 12-month, randomised, sham controlled, double-masked, multicentre Phase II study of safety and efficacy of ranibizumab in DME with central involvement (RESOLVE Study) enrolled 151 subjects to either ranibizumab (0.3 mg, n=51; or 0.5 mg, n =51) or sham treatment (n=49). Two cases of endophthalmitis were reported in the ranibizumab treatment group (2%) and no cases in the sham group (Massin 2010). The total number of injections was not published.

Two 24 month, parallel, methodologically identical, randomised, multicentre, double-masked, sham injection-controlled, Phase III studies (RISE and RIDE) to evaluate efficacy and safety of intravitreal ranibizumab in DME. In RISE, 377 patients were randomised to either ranibizumab (n=125 to 0.3mg and n=125 to 0.5mg) or sham injection (n=127) out of which one case of endophthalmitis occurred in the 0.3mg ranibizumab treatment group (0.8%) and no case of endophthalmitis in 0.5mg ranibizumab and sham group. Total number of injections in sham group was 2,461, 0.3mg ranibizumab was 2682 and 0.5mg ranibizumab was 2,628 in RISE study. In RIDE, 382 patients were randomised to either ranibizumab (n=125 to 0.3mg and n=127 to 0.5mg) or sham injection (n=130) out of which one case of endophthalmitis occurred in the 0.3mg ranibizumab treatment group (0.8%), two cases of endophthalmitis in 0.5mg ranibizumab treatment group (1.6%) and no cases in sham group. Total number of injections in the sham group was 2,647, 0.3mg ranibizumab was 2,560 and 0.5mg ranibizumab was 2,714 in the RIDE study (Nguyen 2012, Boyer 2015).

A 12-month, randomised, laser controlled, double masked, multicentre Phase III study to demonstrate superiority of ranibizumab 0.5 mg monotherapy or combined with laser over laser alone in DME patients

(RESTORE study). 345 patients were randomised to ranibizumab + sham laser (n = 116), ranibizumab + laser (n =118), or sham injections + laser (n = 111). No cases of endophthalmitis were reported in any treatment arms. Total number of injections in ranibizumab + sham laser was 800, ranibizumab + laser was 816 and sham injections + laser were 802 (Mitchell 2011).

A 6-month phase 2 randomised, multicentre clinical trial of intravitreal bevacizumab for DME conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net) at 36 clinical sites in the US reported one case of injection-related endophthalmitis out of 185 injections. In this study 121 patients (109 eligible for analysis) have been randomly assigned to one of five groups: focal photocoagulation at baseline (n=19), intravitreal injection of 1.25 mg bevacizumab at baseline and 6 weeks (n=22), intravitreal injection of 2.5 mg bevacizumab at baseline and 6 weeks (n=24), intravitreal injection of 1.25 mg bevacizumab at baseline and sham injection at 6 weeks (n=22), or intravitreal injection of 1.25 mg bevacizumab at baseline and 6 weeks with photocoagulation at 3 weeks (n=22) (Scott 2007).

In a Phase II randomised double-masked, sham controlled, trial of pegaptanib sodium for DME one case of endophthalmitis out of a total of 652 injections in 128 pegaptanib subjects occurred. The occurrence rate of endophthalmitis was 0.15% per injection or 0.8% per subject assigned to a pegaptanib group. No subject developed endophthalmitis in the sham group (n=42). This 36-week trial enrolled 172 patients with DME from 39 US sites (Cunningham 2005).

Reports from ROP studies

Among 143 premature infants included in a prospective, controlled, randomised, stratified, multicentre trial to assess intravitreal bevacizumab monotherapy for zone I or zone II posterior stage 3+ (i.e., stage 3 with plus disease) ROP (BEAT-ROP), there were no cases of endophthalmitis reported (Mintz-Hittner, 2011).

Impact on individual patient

Endophthalmitis can cause permanent loss of vision if it is not diagnosed at an early stage and appropriately treated. Vision loss as such constitutes a substantial burden for the involved subject.

Risk factors and risk groups:

Improper aseptic technique increases the risk of intraocular inflammation.

Preventability:

Preventing endophthalmitis following intravitreal injections involves a combination of procedural precautions, patient selection criteria, and prophylactic measures:

Sterile Technique: Ensuring strict adherence to sterile technique during the entire injection procedure is paramount. This includes thorough hand hygiene, the use of sterile gloves and drapes, and proper disinfection of the periocular skin and eyelids.

Preparation of Injection Materials: All injection materials, including needles, syringes, and medication vials, should be sterile and handled with care to minimise the risk of contamination. Single-use disposable equipment is preferred.

Antiseptic Eyelid Preparation: Pre-injection antisepsis of the eyelids and periocular skin with an appropriate antiseptic solution (such as povidone-iodine or chlorhexidine) can help reduce the microbial load on the ocular surface.

Use of Prophylactic Antibiotics: Administration of topical or intraocular antibiotics before or after the injection may further reduce the risk of infection.

Patient Selection: Patients with active ocular infections, inflammation, or compromised immune function may be at higher risk of developing endophthalmitis following intravitreal injection. Proper evaluation and selection of patients for injection procedures are essential to minimise risk.

Injection Site Selection: Choosing an appropriate injection site away from areas of active inflammation or infection can help reduce the risk of introducing microorganisms into the eye.

Post-Injection Monitoring: Patients must be educated about the signs and symptoms of endophthalmitis and instructed to report any concerning ocular symptoms promptly. Close follow-up and monitoring after the injection allow for early detection and treatment of potential complications.

Environmental Controls: Maintaining a clean and sterile environment in the injection area, including the use of laminar flow systems in the operating room or clinic, can further reduce the risk of contamination.

Continuous Quality Improvement: Regular audits of injection procedures, feedback mechanisms, and adherence to best practices help ensure ongoing improvement in infection prevention measures.

While these strategies can significantly reduce the risk of endophthalmitis following intravitreal injections, it's important to recognise that the risk can never be completely eliminated. Vigilance, thorough training, and a commitment to maintaining high standards of infection control are essential for optimising patient safety during these procedures. Treating physicians need to be aware of general underlying mechanism to anticipate risks related to locations different from the authorised indication.

Thus, only experienced and appropriately trained ophthalmologists should be charged with the injections.

Moreover, patients should report to their doctors any signs or symptoms of intraocular inflammation (e.g., visual acuity decreased, pain, photophobia, or redness) to enable the treating physician to introduce appropriate countermeasures in due time.

Impact on the risk-benefit balance of the product:

An educational programme is performed as an additional risk minimisation measure to raise patients' and physicians' awareness on identified and potential risks.

This important identified risk does not have an impact on the positive risk-benefit balance of Eyluxvi.

Moreover, patients should report to their doctors any signs or symptoms of intraocular inflammation (e.g., visual acuity decreased, pain, photophobia, or redness) to enable the treating physician to introduce appropriate countermeasures in due time.

Public health impact:

Severe intraocular infection/inflammation such as endophthalmitis can cause permanent loss of vision if it is not rapidly diagnosed and appropriately treated. This condition is likely to impact the ability to work and to increase the dependency on caregivers.

Important Identified Risk: Intraocular inflammation

Potential mechanisms:

In a certain percentage the intraocular inflammation is culture negative. However, there are some difficulties in the definition and diagnosis of "sterile" endophthalmitis or intraocular inflammation. Many infectious cases are not diagnosed as such as no tap is performed, or tap is performed, but culture is false negative. Vice versa, true sterile cases may be false positive in culture (e.g., due to contamination of the medium) and thus misdiagnosed as infectious.

Evidence sources and strength of evidence:

Data from clinical trials, post-marketing surveillance and literature.

Post-injection, sterile intraocular inflammation is a known uncommon to rare adverse event following intravitreal injections of anti-VEGFs and for other intravitreally applied drugs.

The etiology of sterile intraocular inflammations, independently of the administered drug, remains uncertain, and a multifactorial origin has been proposed. Needle trauma per se might cause a certain inflammatory reaction. Inflammation secondary both to IVT triamcinolone acetonide and to IVT bevacizumab (or other anti-VEGF agents) that manifest with acute and painless vision loss is usually interpreted as being primarily toxic and sterile. In these patients, visual acuity improves progressively as the intraocular inflammation reduces without any specific treatment. However, since there remains a substantial uncertainty on origin, the complication is often treated - on top of steroids and NSAID - like an acute (infectious) endophthalmitis with antibiotics because of the devastating visual prognosis of this intraocular infection in the absence of antibiotic therapy.

Characterisation of the risk:

Next to endophthalmitis/intraocular inflammations with an infectious origin, there are inflammations where no pathogens can be identified (either no culture performed or negative culture growth), the condition may be characterised as "sterile" inflammatory condition.

The cause of a sterile inflammation, independently of the administered drug, remains uncertain, and a multifactorial origin cannot be discarded. An intraocular inflammation generally constitutes a serious condition, which may lead to generalised eye inflammation and risk of blindness. Treatment should be initialised as soon as possible, and, depending on cause and severity, may consist of topical and intravitreal application of antibiotics, corticosteroids, and surgical removal of matter and infected structures (drainage, vitrectomy). The proportion of VEGF Trap-Eye-exposed adult patients who experienced intraocular inflammation in the study eye in the clinical studies with VEGF Trap-Eye ranged from 0% to 2.6% (VIEW 1 & 2 AMD studies).

Frequency

AMD - Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks): The incidence of intraocular inflammation in the study eye over 96 weeks in the AMD studies VIEW 1 and VIEW 2 was 2.6% and 3.9% in the combined VEGF Trap-Eye and in the ranibizumab group, respectively.

AMD - VIEW 1 long-term extension study: Intraocular inflammation in the study eye during the extension period occurred in 6 patients in the former randomised VEGF Trap-Eye groups (2.4% or 1.9% based on all treated patients). There were no meaningful differences compared with the frequency of intraocular inflammation reported from the pivotal AMD trials through Week 96.

AMD - Clinical Trial SIGHT (52 weeks): Cases of intraocular inflammation were infrequent in the SIGHT study, since only one patient in the VEGF Trap-Eye 2Q8 group with "vitreal cells" was reported (0.3% of all patients exposed to VEGF Trap-Eye).

AMD - Clinical Trial ALTAIR (52 weeks): No events pertaining to the group of intraocular inflammations (excluding likely infectious origin) in the study eye were reported during the course of the ALTAIR study.

CRVO Clinical Trials COPERNICUS and GALILEO (pooled data. 76/100 weeks) A total of 7 patients (5 [1.6%] of them on treatment with VEGF Trap-Eye) experienced at least one event of IOI in the pooled CRVO studies. In view of the small absolute number of events, no meaningful differences were observed between the 2 randomised treatment groups.

BRVO Clinical Trial VIBRANT (52 weeks: One patient experienced intraocular inflammation events in the Phase III study VIBRANT through Week 52: Two events (preferred term: "vitreal cells") occurred in this

patient in the Laser + VTE 2 mg group (1.1%; N=92), who was also included in the VEGF Trap-Eye total group (0.6%; N=158). The 2 events were mild, non-serious, and resolved.

Myopic CNV Clinical Trial MYRROR (48 weeks'): There was only one patient with intraocular inflammation reported in the MYRROR study through Week 48. This patient was treated in the VEGF Trap-Eye 2 mg group (1.1% [N=91] or 0.9% related to N=116 [VEGF Trap-Eye total group]). The underlying event (PT: Anterior chamber cell) was non-serious, had a mild severity, and was resolved.

DME - Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks): The proportion of patients with IOI in the 2 randomised Phase III DME studies up to Week 148 was 1.0% in the laser group and 2.4% in the VEGF Trap-Eye total group.

DME - Clinical Trial VIVID-EAST (52 weeks): No events pertaining to the group of other intraocular inflammation in the study eye were reported in the VIVID-EAST study.

DME - Open-label Clinical Trial VIVID-JAP AN (52 weeks): In the open-label study VIVID-Japan, one patient was reported to have experienced one intraocular inflammation event (non-serious, mild, and resolved "iritis").

ROP - Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data): No events pertaining to the group of intraocular inflammation in the VEGF Trap-Eye-exposed eye were reported in the FIREFLEYE or the FIREFLEYE NEXT study.

Post-Marketing Data of Eylea

Considering the sales figures and the estimated cumulative patient exposure in the post-marketing period until 30 SEP 2017, the reporting rate of IOI cases (N=1,047) was 0.07 cases per 1,000 sold vials (0.007%) and 0.45 cases per 1,000 patient years (0.045%), respectively. The incidence reported thus far during post-authorisation use is within the reported incidence reported in the literature with the IVT injection of anti-VEGF agents and other drugs (Pospisil 2024).

Information on seriousness and outcome

Most reported cases in the post-marketing data were serious and most reported outcomes were "recovered/resolved".

Background incidence/prevalence

Post-injection, sterile intraocular inflammation is a known risk following intravitreal injections of anti-VEGFs and for other intravitreally applied drugs.

Incidence rates reported in the literature can vary from 0.02% to 0.3% and have been reported to often occur in clusters. In the largest retrospective case series reported to date, Moshfeghi et al. (2012) described 12 cases (11 patients) out of 60,322 anti-VEGF injections (bevacizumab n=7; ranibizumab n=5) that developed post-injection inflammation (0.02% per injection). Day et al. (2011) conducted a retrospective, longitudinal case-control study using the Medicare 5% claims database. Based on an evaluation of 40,903 intravitreal injections of anti-VEGF agents in wet AMD, an endophthalmitis rate of 0.09% (37 cases) and a uveitis rate of 0.11% (45 cases) were reported. Chong et al. (2010) reported 44 cases of sterile inflammation after intravitreal injection of bevacizumab (0.27% of 16,166 injections). Seventeen inflammatory reactions were clustered around specific dates, which suggests a possible relation to drug preparation, though a specific cause remains unclear.

In Ness et al. (2010), a cluster of 10 cases of "toxic vitritis" developed after intravitreal injection of bevacizumab - 6 patients were culture-negative and the remaining 4 were not cultured. The authors

attributed these cases to a toxic reaction from the syringe brand used. No further cases occurred after changing to another brand of syringe.

Roth et al. (2003) described a cluster of 7 patients out of 104 who developed culture negative endophthalmitis, following triamcinolone injection for macula oedema. All 7 cases experienced painless, but severe inflammation within 2 days of intravitreal injection.

Reports from wet AMD. CRVO. BRVO. myopic CNV. DME. and ROP studies

Please see the remarks for previous risk "endophthalmitis".

Impact on individual patient

Severe intraocular infection/inflammation can cause permanent loss of vision, if not diagnosed at an early stage and appropriately treated. Vision loss as such constitutes a substantial burden for the involved subject.

Risk factors and risk groups:

Improper aseptic technique increases the risk of intraocular inflammation.

Preventability:

Measures other than aseptic injection techniques to prevent infectious reactions are not known to minimise the risk of IOI. It is crucial to work under strict aseptic and sterile conditions.

Thus, only experienced and appropriately trained ophthalmologists should be tasked with the injection procedure.

Moreover, patients should report to their doctors any signs or symptoms of intraocular inflammation (e.g., visual acuity decreased, pain, photophobia, or redness) as soon as possible to enable the treating physician to introduce appropriate countermeasures in due time.

Impact on risk-benefit balance of the product

An educational programme is performed as an additional risk minimisation measure to raise patients' and physicians' awareness on identified and potential risks.

This important identified risk does not have an impact on the positive risk-benefit balance of Eyluxvi.

Public health impact

Severe intraocular infection/inflammation can cause permanent loss of vision, if it is not rapidly diagnosed and appropriately treated. This condition is likely to impact the ability to work and to increase the dependency on caregivers.

Important Identified Risk: Transient intraocular pressure increase

Potential mechanisms:

Transient intraocular pressure increase is attributed to an increase in vitreous volume after aflibercept injection (volume effect).

Due to the filling of the eyeball with liquids (i.e., aqueous and vitreous humor), there is an inherent pressure in the eye, which is measured in the same unit as the blood pressure is (i.e., in millimeter Mercury; mmHg). Normal pressure in the inner eye is approximately 10-21 mmHg. Elevated eye pressure is a major risk factor for a condition called "glaucoma", which is characterised by a loss of nerve fibres in the optic nerve with the subsequent risk of blindness. However, many different factors may be responsible for the development of glaucoma, and increased intraocular pressure is not a mandatory

prerequisite for the development of glaucoma (e.g., the condition of normal-tension glaucoma is well-known). In the scope of intravitreal injections, it is easily comprehensible that the volume load caused by the application of the drug, which is dissolved in a certain amount of injection liquid, will lead to a transient increase of intraocular pressure at least until the surplus fluid will have been resorbed from the inner eye.

Evidence source(s) and strength of evidence:

Data from clinical trials, post-marketing surveillance and literature.

Characterisation of the risk:

The proportion of VEGF Trap-Eye-exposed adult patients who experienced an increase in intraocular pressure in the study eye in the clinical studies ranged from 0.5% (ALTERA study) to 13.6% (CRVO studies GALILEO & COPERNICUS).

Post-Marketing Data of Eylea

Considering the sales figures and the estimated cumulative patient exposure in the post-marketing period until 30 SEP 2017, the reporting rate of cases associated with IOP increase (N=250) was 0.02 cases per 1,000 sold vials (0.002%) and 0.11 cases per 1,000 patient years (0.011%), respectively. A total of 106 out of the 260 reported events of increased IOP were regarded as serious. Reported outcomes were "recovered/resolved" in 88 events, "recovering/resolving" in 31 events, and "not recovered/not resolved" in 28 events (missing or unknown outcomes in the remaining 113 events). Transient IOP increase is usually a mild reaction which is compensated within 0.5 - 1 hours after injection so that IOP normalises back to baseline values. Patient usually recover without sequelae (Pospisil 2024).

Risk factors and risk groups:

Patients with glaucoma, increased intraocular pressure is a known adverse drug reaction on treatment with intravitreal corticosteroids.

Preventability:

Intraocular pressure should be checked after each injection. As the transient increase of eye pressure is an inherent result of the procedure-related volume load in the scope of intravitreal injections, there is no reasonable chance to avoid this effect. However, this effect is usually transient, and there is no robust evidence so far that pressure increases following intravitreal injections (even after multiple injections) could become durable or may lead to clinically relevant glaucoma.

Impact on the risk-benefit balance of the product:

An educational programme is performed as an additional risk minimisation measure to raise patients' and physicians' awareness on identified and potential risks.

This important identified risk does not have an impact on the positive risk-benefit balance of Eyluxvi.

Public health impact:

Due to the transient and usually mild nature of the condition, no impact of this safety concern on public health issues is expected.

Important Identified Risk: Retinal pigment epithelial tears

Potential mechanisms:

Development of retinal pigment epithelial (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.

Evidence source(s) and strength of evidence:

Data from clinical trials, post-marketing surveillance and literature.

The retinal pigment epithelium is the outer layer of the retina. Tears in that layer may occur secondary to AMD, following intravitreal injections, or for unknown reasons. These tears may be self-sealing or may require sealing by laser coagulation.

Characterisation of the risk:

In clinical trials up to 1.9% of patients with underlying wet AMD treated with VEGF Trap-Eye developed a tear of the outer layer of the retina, in 10% of these cases the adverse event was considered serious. RPE tears remained unresolved until the end of the study in the majority of the affected patients in any treatment group.

None of the patients with underlying CRVO, BRVO, myopic CNV, or DME developed a tear of the outer layer of the retina.

RPE tears have been reported in patients with wet AMD in the absence of treatment, particularly when a pigment epithelial detachment (PED) is present. Incidence rates for spontaneous RPE tears ranged between 2-6% of eyes with AMD (Chan 2010, Chang 2007, Salz 2010) and between 10-25% in eyes with AMD and pigment epithelial detachments (PED, Salz 2020). The most important predisposing risk factor appears to be PED size as measured by basal diameter (Chang 2007) and vertical height (Chan 2010, Pauleikhoff 2002). Furthermore, eyes with serious RPE detachment appear to be more vulnerable to RPE tears (Ronan 2007).

Development of retinal pigment epithelial (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 neovascularisation.

Preventability:

The underlying mechanisms resulting in RPE tears following intravitreal injection are not yet understood and thus, no preventive measures are currently known.

Impact on the risk-benefit balance of the product:

An educational programme is performed as an additional risk minimisation measure to raise patients' and physicians' awareness on identified and potential risks.

This important identified risk does not have an impact on the positive risk-benefit balance of Eyluxvi.

Public health impact:

The potential public health impact of this safety concern is low due to the low frequency of serious or severe events in clinical trials.

Important Identified Risk: Cataract (especially of traumatic origin)

Potential mechanisms:

Related to the intravitreal procedure.

Evidence source(s) and strength of evidence:

Data from clinical trials, post-marketing surveillance and literature.

Generally, clouding of the usually clear eye lens is called a cataract. Cataract may occur spontaneously (particularly in the elderly), as a side effect of certain drugs, or following outside influences such as irradiation or mechanical injury (traumatic cataract).

If the needle used to inject aflibercept touched the lens in the patient's eye this could cause such a traumatic cataract. There is currently no evidence that the occurrence of a traumatic cataract is increased on treatment with aflibercept. However, as this might be a hypothetical result of the lens perforation, it has been included as potential important risk.

Characterisation of the risk:

The proportion of aflibercept-exposed adult patients who experienced traumatic cataract in the study eye in the clinical studies with VEGF Trap-Eye ranged from 0% to 2.8% (VIVID-DME & VISTA-DME).

Post-Marketing Data of Eylea

Considering the sales figures and the estimated cumulative patient exposure in the post-marketing period until 30 SEP 2017, the reporting rate of "cataract" cases was 0.04 cases per 1,000 sold vials (0.004%) and 0.31 cases per 1,000 patient years (0.031%), respectively. Most of the reported cataract events were serious (Poposil 2024).

Information from literature

Historically, traumatic cataract (TC) has been reported in patients receiving IVT injections, but limited information is available about cataract development or progression after intravitreal injection of VEGF inhibitors. In addition, due to differences in the way cataract and/or “traumatic cataract” have been defined or reported in such studies, the direct comparison of some reported rates could be difficult. Special attention should be given to the type of cataract the reported rates represent.

Impact on individual patient

Development of cataract may impair vision and thus may require cataract surgery to remove the lens opacification.

Risk factors and risk groups:

Cataract is a known adverse drug reaction on treatment with intravitreal application of corticosteroids.

Preventability:

By correct IVT procedure and a correct angle of the needle while injecting a cataract could be prevented. This is common knowledge of injecting physicians.

Impact on the risk-benefit balance of the product:

An educational programme is performed as an additional risk minimisation measure to raise patients' and physicians' awareness on identified and potential risks.

This important identified risk does not have an impact on the positive risk-benefit balance of Eyluxvi.

Public health impact:

Patients experiencing (traumatic) cataract may require cataract surgery.

Important Potential Risk: Medication errors

Potential mechanisms:

Not applicable.

Evidence source(s) and strength of evidence:

Data from clinical trials, post-marketing surveillance and literature.

The Eyluxvi vial is for single use. Thus, injecting the entire volume of the vial would result in overdose. However, this numerical overdose is limited to about double dose. Furthermore, the drug will be administered only by qualified physicians (not by patients) reducing 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.

Characterisation of the risk:

Post-Marketing Data of Eylea

In view of the large number of Eylea vials sold by 15 SEP 2017 (almost 16 million), there is no indication that medication errors might be a relevant issue of treatment with Eylea in routine care. Numerically, the reporting rate of cases with medication error (N=3,245, 3,577 events) was 0.20 cases per 1,000 sold vials (0.020%) and 1.40 cases per 1,000 patient years of exposure (0.140%), respectively.

The 5 most frequently reported preferred term events were “inappropriate schedule of drug administration” (1,476 events), “drug dose omission” (583 events), “product use issue” (523 events), “multiple use of single-use product” (263 events), and “product use in unapproved indication” (172 events).

Vial/dose fractioning (coded to PT “multiple use of single-use product”) is a common practice in some countries, and it might be supported by some health insurances. This PT was reported in 263 cases (with 263 events) and more than half of these cases (138 cases) were invalid, while 125 cases were valid. Most of the valid cases were associated with intraocular inflammations/infections which is an established and labelled ADR of the VEGF Trap-Eye injection. For these cases it remains unknown whether the procedure of vial splitting contributed to the development of an intraocular infection. Overall, no increase in reporting rates for reported intraocular inflammations/infections was observed over the years worldwide, and to date, the reported number of cases with vial fractioning is considered low.

A few of the reported medication error cases were considered serious (49 cases [1.5% of all 3,245 cases] with 52 events [1.5% of all 3,577 events].

For most of the 3,577 cases, the event outcome was unknown or not reported (3,283 events). Specified event outcomes were “recovered/resolved” (159 events), “recovering/resolving” (21 events), “recovered/resolved with sequelae” (one event), and “not recovered/not resolved” (113 events) (Pospisil 2024).

Impact on individual patient

There is no life-threatening potential when Eyluxvi is administered by an incorrect route.

Risk factors and risk groups:

Not applicable.

Preventability:

Instructions on the correct drug preparation and administration will be given in the SmPC and the educational programme to minimise the risk of accidental medication errors.

Impact on the risk-benefit balance of the product:

An educational programme is performed as an additional risk minimisation measure to raise patients' and physicians' awareness on identified and potential risks.

This important potential risk does not have an impact on the positive risk-benefit balance of Eyluxvi.

Public health impact:

There is no life-threatening potential when Eyluxvi is administered by an incorrect route.

Important Potential Risk: Off-label use and misuse

Potential mechanisms:

Not applicable.

Evidence source(s) and strength of evidence:

Post-marketing surveillance and literature.

As with other drugs, Eyluxvi 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 Eyluxvi in such off-label use will be limited any case of off-label use will be considered a potential risk. Since Eyluxvi has no dependence potential, the risk of misuse is regarded as very low.

Characterisation of the risk:

Post-Marketing Data of Eylea

Considering the sales figures and the estimated cumulative patient exposure of Eylea in the post-marketing period until 30 SEP 2017, the reporting rate of off-label cases (N=1,846) was 0.12 cases per 1,000 sold vials (0.012%) and 0.80 cases per 1,000 patient years (0.080%), respectively.

A review of these cases suggested that many cases of off-label use and misuse occurred within a labelled indication and were solely associated with deviations from the labelled treatment schedule or were used for indications that were not yet approved locally at the time of their use (but were approved elsewhere) (Pospisil 2024).

Impact on individual patient

There is no life-threatening potential when Eyluxvi is administered by an incorrect route.

Risk factors and risk groups:

Not applicable.

Preventability:

Intentional misuse, as such, is difficult to prevent because of the user's deliberate decision to deviate from the provided instructions. However, there is no known dependence potential of Eyluxvi.

Impact on the risk-benefit balance of the product:

An educational programme is performed as an additional risk minimisation measure to raise patients' and physicians' awareness on identified and potential risks.

This important potential risk does not have an impact on the positive risk-benefit balance of Eyluxvi.

Public health impact:

Not applicable.

Important Potential Risk: Embryo-fetotoxicity

Potential mechanisms:

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.

Evidence sources and strength of evidence:

Data from clinical trials, post-marketing surveillance and literature.

Testing of aflibercept in animals was performed as a standard part of the development of Eylea. It was noted that aflibercept given in extremely high doses to animals (by far exceeding the doses which would be given to humans) might have an adverse influence on prenatal development (i.e., during the embryonic or fetal development period; so-called embryo-fetotoxicity). Therefore, embryo-fetotoxicity is regarded as a potential risk of treatment with aflibercept. However, Eyluxvi is injected locally and at a dose that is distinctively lower than the exposure in animals under which the critical events were observed. So far, there is no relevant indication that treatment with Eyluxvi might be associated with embryo-fetotoxicity.

Characterisation of the risk:

Overall, the few pregnancy cases currently reported both in clinical studies and in post-marketing use do not give any rise to assume that treatment with aflibercept might be associated with relevant embryo-fetotoxic effects.

Impact on individual patient

Based on currently available non-clinical data, no individual impact in terms of risk to the treated population is apparent.

Risk factors and risk groups:

Patients at risk are women of childbearing potential.

Preventability:

Treatment with Eyluxvi is not recommended during pregnancy, unless the potential benefit outweighs the potential risk to the fetus.

Impact on the risk-benefit balance of the product:

An educational programme is performed as an additional risk minimisation measure to raise patients' and physicians' awareness on identified and potential risks.

This important potential risk does not have an impact on the positive risk-benefit balance of Eyluxvi.

Public health impact:

Based on currently available non-clinical data, no public health impact in terms of risk to the treated population is apparent.

Part II: Module SVIII - Summary of the safety concerns

The safety concerns (important identified risks, important potential risks, missing information) as identified in previous Modules SII, SIV, SVI, and SVII of Part II are summarised in the following Table SVIII.1. Pharmacovigilance actions associated with these safety concerns are provided in Part III (Pharmacovigilance plan).

Table SVIII.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	• None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include the use of specific adverse drug reaction follow-up questionnaires for cases of endophthalmitis and intraocular inflammation (see Annex 4).

III.2 Additional pharmacovigilance activities

No non-clinical, clinical or epidemiological (non-interventional or interventional) studies are planned.

III.3 Summary Table of additional Pharmacovigilance activities

No non-clinical, clinical or epidemiological (non-interventional or interventional) studies are planned.

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are planned.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Endophthalmitis (likely infectious origin)	**Routine risk communication:** SmPC section 4.2 (Posology and method of administration) SmPC section 4.3 (Contraindications) SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) Package Leaflet section 2 (What you need to know before you are given Eyluxvi) Package Leaflet section 3 (How you will be given Eyluxvi) Package Leaflet section 4 (Possible side effects) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** In SmPC Section 4.2 (Posology and method of administration): A comprehensive description of the injection procedure (including short-term follow-up) is provided for ensuring high-quality standard of the intervention. In SmPC Section 4.2 (Posology and method of administration) and Package Leaflet section 2 (What you need to know before you are given Eyluxvi): Suggestive symptoms of endophthalmitis are mentioned. *Ocular or periocular infection* and *active severe intraocular inflammation* are listed in SmPC Section 4.3 (Contraindications) and Package Leaflet section 2 *(*What you need to know before you are given Eyluxvi). SmPC Section 4.4 (Special warnings and precautions for use): Instructions for aseptic injection techniques, monitoring and instructions of patients are mentioned. Package Leaflet section 2 (What you need to know before you are given Eyluxvi):Description of symptoms potentially indicative of endophthalmitis is given. Package Leaflet section 3 (How you will be given Eyluxvi): Description on pre-injection use of disinfectant for cleaning measures is provided.

	Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections.
Intraocular inflammation	**Routine risk communication:** SmPC section 4.2 (Posology and method of administration) SmPC section 4.3 (Contraindications) SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) Package Leaflet section 2 (What you need to know before you are given Eyluxvi) Package Leaflet section 3 (How you will be given Eyluxvi) Package Leaflet section 4 (Possible side effects) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** In SmPC Section 4.2 (Posology and method of administration): A comprehensive description of the injection procedure (including short-term follow-up) is provided for ensuring high-quality standard of the intervention. *Ocular or periocular infection* and *active severe intraocular inflammation* are listed in SmPC Section 4.3 (Contraindications) and Package Leaflet section 2 *(*What you need to know before you are given Eyluxvi). SmPC Section 4.4 (Special warnings and precautions for use): Instructions for aseptic injection techniques, monitoring and instructions of patients are given. SmPC Section 4.4 (Special warnings and precautions for use): Potential for immunogenicity with Eyluxvi is mentioned (see Section 4.8). Monitoring of symptoms is advised. Package Leaflet section 2 (What you need to know before you are given Eyluxvi): Description, monitoring and early treatment of symptoms are described. Package Leaflet section 3 (How you will be given Eyluxvi): Description on pre-injection use of disinfectant for cleaning measures is provided. **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections.

Transient intraocular pressure increase	**Routine risk communication:** SmPC section 4.2 (Posology and method of administration) SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) SmPC section 4.9 (Overdose) Package Leaflet section 2 (What you need to know before you are given Eyluxvi) Package Leaflet section 4 (Possible side effects) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 (Posology and method of administration): Appropriate monitoring for elevation in intraocular pressure is mentioned. Special precaution in patients with poorly controlled glaucoma is mentioned. SMPC Section 4.9 (Overdose): Effect of overdosing, monitoring and treatment of intraocular pressure by the physician are mentioned. Package Leaflet section 2 (What you need to know before you are given Eyluxvi): Injections with Eylea may cause an increase in eye pressure. **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections.
Retinal pigment epithelial tears	**Routine risk communication:** SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) Package Leaflet section 2 (What you need to know before you are given Eyluxvi) Package Leaflet section 4 (Possible side effects) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 (Special warnings and precautions for use): A description of risk factors is given for retinal pigment epithelial tear (RPE tear) in wet AMD patients and advice to be cautious when initiating Eyluxvi therapy in patients with this risk factor. Package Leaflet section 2 (What you need to know before you are given Eyluxvi): Check of risk factors for retinal tear/detachment, RPE tear/detachment by the physician is mentioned. **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections.

Cataract (especially of traumatic origin)	**Routine risk communication:** SmPC section 4.2 (Posology and methods of administration) SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) Package Leaflet section 2 (What you need to know before you are given Eyluxvi) Package Leaflet section 3 (How you will be given Eyluxvi) Package Leaflet section 4 (Possible side effects) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** In SmPC Section 4.2 (Posology and method of administration): A comprehensive description of the injection procedure (including short- term follow-up) is provided for ensuring high-quality standard of the intervention. SmPC Section 4.4 (Special warnings and precautions for use): Instructions for aseptic injection techniques, monitoring and instructions of patients are given. Package Leaflet section 2 (What you need to know before you are given Eyluxvi): Description, monitoring and early treatment of symptoms are described. Package Leaflet section 3 (How you will be given Eyluxvi): Description on pre-injection use of disinfectant for cleaning measures is provided. **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections.
Medication errors	**Routine risk communication:** SmPC section 4.2 (Posology and methods of administration) SmPC section 4.9 (Overdose) Package Leaflet section 1 (What Eyluxvi is and what it is used for) Package Leaflet section 3 (How you will be given Eyluxvi) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** In SmPC Section 4.2 (Posology and methods of administration) and Package Leaflet section 'information intended for HCPs only': Verbal instruction is provided for the handling of the vial for minimising the risk of drug administration error. SmPC Section 4.9 (Overdose): Association between overdose and IOP increase is mentioned. **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections.

Off-label use and misuse	**Routine risk communication:** SmPC section 4.1 (Therapeutic indications) SmPC section 4.2 (Posology and methods of administration) SmPC section 4.3 (Contraindications) SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.6 (Fertility, pregnancy and lactation) Package Leaflet section 1 (What Eyluxvi is and what it is used for) Package Leaflet section 2 (What you need to know before you are given Eyluxvi) Package Leaflet section 3 (How you will be given Eyluxvi) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Contraindications are listed in SmPC Section 4.3 (Contraindications) and Package Leaflet section 2 (What you need to know before you are given Eyluxvi): Conditions in which treatment should be withheld/discontinued/not recommended are included in the SmPC section 4.4 and Package Leaflet section 2 (What you need to know before you are given Eyluxvi). Conditions of use in pregnancy and breastfeeding are included in the SmPC section 4.6 and Package Leaflet section 2 (What you need to know before you are given Eyluxvi). **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections.
Embryo-fetotoxicity	**Routine risk communication:** SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.6 (Fertility, pregnancy and lactation) SmPC section 5.3 (Preclinical safety data) Package Leaflet section 2 (What you need to know before you are given Eyluxvi) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 (Special warnings and precautions for use), SmPC section 4.6 (Fertility, pregnancy and lactation) and Package Leaflet section 2 (What you need to know before you are given Eyluxvi): Instructions for pregnancy and women of childbearing potential are provided. **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections.

V.2. Additional Risk Minimisation Measures

Additional risk minimisation: Educational programme

Besides routine risk minimisation activities (SmPC and patient information), additional activity, specifically an educational programme, is considered to be necessary for the important identified risks of endophthalmitis (likely infectious origin), intraocular inflammation, transient intraocular pressure increase, retinal pigment epithelium tears, and cataract (especially of traumatic origin), as well as for the important potential risk of medication errors, off-label use and misuse, and embryo-fetotoxicity.

Objectives and rationale for the additional risk minimisation activity:

Informing patients and physicians about risks for minimising their occurrence and consequences in routine care and include guidance on the IVT injection procedure. Educational material also includes guidance on the IVT injection procedure to re-train physicians for minimising injection-related adverse reactions. The following risks are addressed in the Educational Material: endophthalmitis/intraocular inflammation, transient intraocular pressure increase, RPE tear, cataract, medication error, off label use and misuse, and embryo-fetotoxicity.

The target audience are HCPs specialised in intravitreal injections of anti-VEGF agents as well as patients to be treated. The key messages of the educational materials (provided in Part VII Annex 6) will be distributed as paper version and/or through a digital communication method (digital platform) to the target audience(s). The feasibility and implementation of the planned distribution path will be agreed upon with and after liaising with the national health authorities in the member states, as requested per GVP Module XVI addendum.

Target audience and planned distribution path:

The target audience are HCPs specialised in intravitreal injections of anti-VEGF agents as well as patients to be treated. The key messages of the educational materials (provided in Part VII Annex 6) will be distributed as paper version and/or through a digital communication method (digital platform) to the target audience(s). The feasibility and implementation of the planned distribution path will be agreed upon with and after liaising with the national health authorities in the member states, as requested per GVP Module XVI addendum.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Endophthalmitis (likely infectious origin)	**Routine risk minimisation measures:** SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet sections 2, 3, and 4 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaires are

	only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimisation measures:** Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video) and patient guide "Your guide to Eyluxvi" and its audio version).	used for enhanced pharmacovigilance monitoring of endophthalmitis/intraocular inflammation cases (see Annex 4). **Additional pharmacovigilance activities:** None
Intraocular inflammation	**Routine risk minimisation measures:** SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet sections 2, 3, and 4 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimisation measures:** Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video) and patient guide "Your guide to Eyluxvi" and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaires are used for enhanced pharmacovigilance monitoring of endophthalmitis/intraocular inflammation cases (see Annex 4). **Additional pharmacovigilance activities:** None
Transient intraocular pressure increase	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4, 4.8, and 4.9 Package Leaflet sections 2 and 4 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimisation measures:** Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video) and patient guide "Your guide to Eyluxvi" and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None
Retinal pigment epithelial tears	**Routine risk minimisation measures:**	**Routine pharmacovigilance activities beyond**

	SmPC sections 4.4, and 4.8 Package Leaflet sections 2 and 4 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimisation measures:** Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video) and patient guide "Your guide to Eyluxvi" and its audio version).	**adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None
Cataract (especially of traumatic origin)	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4, and 4.8 Package Leaflet sections 2, 3, and 4 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimisation measures:** Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video) and patient guide "Your guide to Eyluxvi" and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None
Medication errors	**Routine risk minimisation measures:** SmPC sections 4.2 and 4.9 Package Leaflet section 1 and 3 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimisation measures:** Educational programme: Beyond routine minimisation activities, additional measures are currently needed to	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None

	raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video) and patient guide "Your guide to Eyluxvi" and its audio version).	
Off-label use and misuse	**Routine risk minimisation measures:** SmPC sections 4.1, 4.2, 4.3, 4.4, and 4.6 Package Leaflet sections 1, 2, and 3 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimisation measures:** Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video) and patient guide "Your guide to Eyluxvi" and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None
Embryo-fetotoxicity	**Routine risk minimisation measures:** SmPC sections 4.4, 4.6, and 5.3 Package Leaflet section 2 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimisation measures:** Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video) and patient guide "Your guide to Eyluxvi" and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None

Part VI: Summary of the risk management plan

Summary of risk management plan for Eyluxvi

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

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

This summary of the RMP for Eyluxvi (aflibercept) should be read in the context of all the 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 Eyluxvi's RMP.

I. The medicine and what it is used for

Eyluxvi (aflibercept) 40 mg/mL solution for injection in a vial 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),
- visual impairment due to myopic choroidal neovascularisation (myopic CNV).

It contains aflibercept as the active substance and it is given by intravitreal injection only.

Further information about the evaluation of Eyluxvi's benefits can be found in Eyluxvi'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/eyluxvi).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

Measures to minimise 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 authorised 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 minimise its risks

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

In the case of Eyluxvi, these measures are supplemented with *additional risk minimisation 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 Eyluxvi is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Eyluxvi are risks that need special risk management activities to further investigate or minimise 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 Eyluxvi. 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).

List of Important Risks and Missing Information	
Important identified risk	• Endophthalmitis (likely infectious origin) • Intraocular inflammation • Transient intraocular pressure increase • Retinal pigment epithelial tears • Cataract (especially of traumatic origin)
Important identified risk	• Medication errors • Off-label use and misuse • Embryo-fetotoxicity
Missing Information	• None

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

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 endophthalmitis.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet sections 2, 3 and 4 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimisation measures:** Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; in addition to patient guide "Your guide to Eyluxvi" and its audio version).
Pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaires are used for enhanced pharmacovigilance monitoring of endophthalmitis/intraocular inflammation cases (see Annex 4). **Additional pharmacovigilance activities:** None

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 minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet sections 2, 3, and 4 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimisation measures:** Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; in addition to patient guide "Your guide to Eyluxvi" and its audio version).
Pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaires are used for enhanced pharmacovigilance monitoring of endophthalmitis/intraocular inflammation cases (see Annex 4). **Additional pharmacovigilance activities:** None

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 Eyluxvi 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 minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8, and 4.9 Package Leaflet sections 2 and 4 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimisation measures:** Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; in addition to patient guide "Your guide to Eyluxvi" 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 Retinal pigment epithelial (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 neovascularisation.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 Package Leaflet sections 2 and 4 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimisation measures:** Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; in addition to patient guide "Your guide to Eyluxvi" 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 minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8 Package Leaflet sections 2, 3, and 4 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimisation measures:** Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; in addition to patient guide "Your guide to Eyluxvi" and its audio version).

Important potential Risk: Medication errors	
Evidence for linking the risk to the medicine	Although Eyluxvi is provided in single use vial, there is an excess volume exceeding the recommended net dose of 2 mg Eyluxvi per injection. Thus, injecting the entire volume of the vial would result in overdose. However, this numerical overdose is limited, and the drug will be administered only by qualified physicians (not by patients). 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 minimisation measures	Routine risk minimisation measures: SmPC sections 4.2 and 4.9 Package Leaflet sections 1 and 3 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections.

	Additional risk minimisation measures: Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; in addition to patient guide "Your guide to Eyluxvi" and its audio version).

Important potential Risk: Off-label use and misuse	
Evidence for linking the risk to the medicine	As with other drugs, Eyluxvi 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 Eyluxvi in such off-label use will be limited any case of off-label use will be considered a potential risk. Since Eyluxvi has no dependence potential, the risk of misuse is regarded as very low.
Risk factors and risk groups	Not applicable
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.1, 4.2, 4.3, 4.4, and 4.6 Package Leaflet sections 1, 2, and 3 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimisation measures:** Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; in addition to patient guide "Your guide to Eyluxvi" and its audio version).

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 minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.6, and 5.3 Package Leaflet section 2 **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimisation measures:** Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; in addition to patient guide "Your guide to Eyluxvi" and its audio version).

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Eyluxvi.

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

There are no studies required for Eyluxvi.

Part VII: Annexes

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Annex 4 - Specific adverse drug reaction follow-up forms

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Annex 4.1: Endophthalmitis and intraocular inflammation (IOI) following the use of Eyluxvi 40 mg/mL (2 mg dose)

Eyluxvi (Aflibercept) Questionnaire – Endophthalmitis / Intraocular inflammation

SECTION I- REFERENCE ID				
BIOLITEC CASE ID:	STUDY ID:	PATIENT ID:		
SECTION II- REPORTER/PATIENT INFORMATION				
Reporter Contact Information				
Reporter: ☐ **Physician** ☐ **Nurse** ☐ **Other (specify):**				
Name:				
Institution / Practice Name				
Address:				
E-mail Address:				
Telephone Number:				
Fax Number:				
Patient Information				
Age: _____years (at onset of the event)	Age group: _____	Gender: ☐ Male ☐ Female	Weight: _____ ☐ kg ☐ lb	Height:_____ ☐ cm ☐ inch
Race: ☐ White ☐ Black ☐ Asian ☐ Other (specify: _____)				
SECTION III- PRODUCT INFORMATION (Eyluxvi)				
Therapy date (dd-mmm-yyyy):_____ ☐ ongoing Number of Eyluxvi doses before the event: _____				
Indication: _____ If other indication, specify: _____				
Eye injected / dose ☐ OS ☐ 2mg ☐ Other (specify: _____) ☐ OD ☐ 2mg ☐ Other (specify: _____)				
Lot / Batch number: OS: _____ Expiry date (dd-mmm-yyyy): _____ OD: _____ Expiry date (dd-mmm-yyyy): _____				
Was the same vial used for more than one patient? ☐ Yes ☐ No If yes, did an event occur in other patients? ☐ Yes ☐ No If yes, how many? _____				
Was the vial aliquoted in several syringes? ☐ Yes ☐ No Was the vial multi punctured? ☐ Yes ☐ No				
Was the supplied filter needle used? ☐ Yes ☐ No ☐ Unknown				
Date of injection preparation (dd-mmm-yyyy): _____ Time of injection preparation (hh:mm): _____				
What was used for injection? Injection needle Batch No.: _____ Brand of the needle: OS _____, OD _____ Syringe (Luer lock: ☐ Yes ☐ No) ☐ Glass ☐ Plastic Batch No.: _____ Brand of the syringe: OS _____, OD _____				
Where was the syringe for injection prepared? ☐ Off-site pharmacy ☐ On-site pharmacy ☐ Treatment / Examining room				
If prepared in pharmacy, provide the name and contact details.: _____				
How many hours did the prepared syringe stay at room temperature prior to administration? _____				

Eyluxvi (Aflibercept) Questionnaire – Endophthalmitis / Intraocular inflammation

SECTION IV- ADVERSE EVENT INFORMATION

Event (as reported term): _____ ☐ OS ☐ OD ☐ OU

Start date / time (dd-mmm-yyyy / hh:mm): _____
or how much time after injection did the event occur (approx.): _____

Stop date (dd-mmm-yyyy): _____
If stop date is unknown, provide the approximate event duration (days): _____

Outcome ☐ recovered ☐ not recovered ☐ resolving ☐ recovered with sequelae ☐ fatal ☐ UNK
If AE resolved / is resolving, did the visual acuity (VA) recover to: ☐ same level before AE started ☐ VA is worse

Clinical presentation:

Treatment of adverse event

Treatment provided: ☐ Yes ☐ No
If yes, specify: ☐ Antibiotics:
☐ Steroids (regimen details):
☐ Surgery (vitrectomy): _____ & date (dd-mmm-yyyy): _____
☐ Unknown

☐ Culture taken on: date (dd-mmm-yyyy): _____
From ☐ OS ☐ OD ☐ OU
Positive for: ☐ OS ☐ OD ☐ OU
Negative for: ☐ OS ☐ OD ☐ OU
☐ Culture not taken / unknown

Reporter causality comment:

The event is considered:
☐ Related to Eyluxvi
☐ Related to intravitreal injection procedure
☐ Not related to Eyluxvi or intravitreal injection procedure

Alternative explanation (e.g. underlying disease / condition predisposing to the event): _____

Action taken with product

	Date from (dd-mmm-yyyy)	Date to (dd-mmm-yyyy)
☐ Does not changed	N/A	N/A
☐ Stopped		N/A
☐ Dose reduced (New dose: ____mg)		
☐ Interrupted		
☐ Unknown	N/A	N/A

Did the event abate/stop after treatment stopped? ☐ Yes ☐ No ☐ Unknown

Did the event reoccur upon resuming treatment? ☐ Yes ☐ No ☐ Unknown

Relevant Clinical Symptoms (to AE of interest). Please indicate which eye was affected.

Signs or symptoms	Start date (dd-mmm-yyyy)	Stop date (dd-mmm-yyyy)

Additional Questions:
Did the patient experience the same event(s) in the past? ☐ Yes ☐ No ☐ Unknown
If yes, please provide relevant details:

Eyluxvi (Aflibercept) Questionnaire – Endophthalmitis / Intraocular inflammation

SECTION V- RELEVANT (intravitreal) CONCOMITANT / HISTORICAL MEDICATION

Drug Name	From (dd-mmm-yyyy)	To (dd-mmm-yyyy)	Ongoing	Dose / No. of injections	Indication	Similar event occurred? If yes, please specify
☐ Anti VEGF Please specify: _____ ☐ OS ☐ OD ☐ OU			☐			
☐ Other Please specify: _____ ☐ OS ☐ OD ☐ OU			☐			

SECTION VI- RELEVANT MEDICAL HISTORY / RISK FACTORS (relevant to the reported event)

Condition	From (dd-mmm-yyyy)	To (dd-mmm-yyyy)	Ongoing
☐ Diabetes			☐
☐ Autoimmune disease, please specify: _____			☐
☐ Malignancy, please specify: _____			☐
☐ Immunodeficiency, please specify: _____			☐
☐ Other, please specify: _____			☐

SECTION VII- ADDITIONAL INFORMATION (COMMENT) (e.g. gender information if not male / female):

Cause of death (if selected outcome was fatal)	Date of death (dd-mmm-yyyy)	Autopsy done	Autopsy details (continue with SECTION IV)
		☐	

This section can also be used to provide information on any of the sections above. Please note the relevant section number below.

Reporter's Signature:	
Date of signature (dd-mmm-yyyy):	

Annex 6 - Details of proposed additional risk minimisation activities

Draft key messages of the additional risk minimisation measures

Eyluxvi (Aflibercept) EU Educational Material - KEY MESSAGES

The MAH commits to provide EU Educational Material for Eyluxvi. Prior to launch and during the product's lifecycle in each Member State the Marketing Authorisation Holder (MAH) will agree the final Educational Material with the National Competent Authority. The MAH ensures that, following discussions and agreement with the National Competent Authorities in each Member State where Eyluxvi is marketed, ophthalmological clinics where Eyluxvi is expected to be used are provided with an updated physician information pack containing the following elements:

- Physician information
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information packs

The physician information in the educational material contains the following key elements:

- Techniques for the intravitreal injection including use of a 30 G needle, and angle of injection
- The vial is for single use only
- The need to expel excess volume of the syringe before injecting Eyluxvi to avoid overdose
- Patient monitoring after intravitreal injection including monitoring for visual acuity and increase of intraocular pressure post-injection
- Key signs and symptoms of intravitreal injection related adverse events including endophthalmitis, intraocular inflammation, increased intraocular pressure, retinal pigment epithelial tear and cataract
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eyluxvi

The patient information pack of the educational material for the adult population includes a patient information guide and its audio version that contain following key elements:

- Patient information leaflet
- Who should be treated with Eyluxvi
- How to prepare for Eyluxvi treatment
- What are the steps following treatment with Eyluxvi
- Key signs and symptoms of serious adverse events including endophthalmitis, intraocular inflammation, intraocular pressure increased, retinal pigment epithelial tear and cataract
- When to seek urgent attention from their health care provider
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eyluxvi