EU Risk Management Plan (RMP) for OPUVIZ (Aflibercept)

RMP version to be assessed as part of this application:

RMP version number:	1.1
Data lock point for this RMP:	Feb 21, 2024
Date of final sign off:	Mar 12, 2024

Rationale for submitting an updated RMP: To update the content of routine risk minimisation and additional risk minimisation measures.

Summary of significant changes in this RMP: The details of routine risk minimisation measures are updated and additional risk minimisation measure is added to align with the originator RMP.

Other RMP versions under evaluation: None.

Details of the currently approved RMP:

Version number:	Not applicable.
Approved with procedure:	Not applicable.
Date of approval (opinion date):	Not applicable.

QPPV name: John Hart

The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

TABLE OF CONTENTS

List of Tables 3
List of Abbreviations 4
Part I: Product(s) overview 5
Part II: Module SI - Epidemiology of the indication(s) and target population(s) 8
Part II: Module SII - Non-clinical part of the safety specification 9
Part II: Module SIII - Clinical trial exposure 12
Part II: Module SIV - Populations not studied in clinical trials 14
SIV.1 Exclusion criteria in pivotal clinical studies within the development programme 14
SIV.2 Limitations to detect adverse reactions in clinical trial development programmes 16
SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes 17
Part II: Module SV - Post-authorisation experience 18
Part II: Module SVI - Additional EU requirements for the safety specification 19
Part II: Module SVII - Identified and potential risks 20
SVII.1 Identification of safety concerns in the initial RMP submission 20
SVII.2 New safety concerns and reclassification with a submission of an updated RMP 21
SVII.3 Details of important identified risks, important potential risks, and missing information 22
Part II: Module SVIII - Summary of the safety concerns 34
Part III: Pharmacovigilance Plan (including post-authorisation safety studies) 35
III.1 Routine pharmacovigilance activities 35
III.2 Additional pharmacovigilance activities 35
III.3 Summary table of additional pharmacovigilance activities 35
Part IV: Plans for post-authorisation efficacy studies 36
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities) 37
V.1 Routine Risk Minimisation Measures 37
V.2 Additional Risk Minimisation Measures 44
V.3 Summary of risk minimisation measures 46
Part VI: Summary of the risk management plan 51
II.A List of important risks and missing information 52
II.B Summary of important risks 52
II.C Post-authorisation development plan 59
II.C.1 Studies which are conditions of the marketing authorisation 59
II.C.2 Other studies in post-authorisation development plan 59

Part VII: Annexes 60
Annex 1 – EudraVigilance interface 61
Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme 62
Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan 63
Annex 4 - Specific adverse drug reaction follow-up forms 64
Annex 5 - Protocols for proposed and ongoing studies in RMP part IV 65
Annex 6 - Details of proposed additional risk minimisation activities (if applicable) 66
Annex 7 - Other supporting data (including referenced material) 68
Annex 8 – Summary of changes to the risk management plan over time 70

LIST OF TABLES

Table Part I.1: Product(s) overview 5
Table SIII.1: Duration of exposure to investigational product (Safety Set 1) 12
Table SIII.2: Demographic characteristics by treatment groups (Randomised Set) 13
Table SIV.1: Exposure of special populations included or not in clinical trial development programmes 17
Table SVII.1: Number and frequency of cataract TEAEs in the study eye from the Phase III study SB15-3001 (Safety Set 1) 29
Table SVIII.1: Summary of safety concerns 34
Table Part V.1: Description of routine risk minimisation measures by safety concern 37
Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern 46

LIST OF ABBREVIATIONS

AMD	age-related macular degeneration
ATC	anatomical therapeutic chemical classification
AUC	area under the plasma concentration-time curve
BP	blood pressure
C_{max}	maximum plasma concentration
CNV	choroidal neovascularisation
DME	diabetic macular oedema
DNA	deoxyribonucleic acid
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
Fc	fragment crystallisable
IgG1	immunoglobulin G1
INN	international nonproprietary name
IOP	intraocular pressure
IP	investigational product
IV	intravenous
MAH	marketing authorisation holder
max	maximum
min	minimum
PL	Package Leaflet
PlGF	placental growth factor
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
RPE	retinal pigment epithelial
RVO	retinal vein occlusion
SC	subcutaneous
SD	standard deviation
SmPC	Summary of Product Characteristics
VEGF	vascular endothelial growth factor
VEGF-A	vascular endothelial growth factor A
VEGFR-1	vascular endothelial growth factor receptor 1
VEGFR-2	vascular endothelial growth factor receptor 2

Part I: Product(s) overview

Table Part I.1: Product(s) overview

Active substance(s) (INN or common name)	Aflibercept
Pharmacotherapeutic group(s) (ATC Code)	S01LA05
Marketing Authorisation Applicant	Samsung Bioepis NL B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	OPUVIZ
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Aflibercept is a recombinant fusion protein consisting of portions of human vascular endothelial growth factor (VEGF) receptor 1 (VEGFR-1) and 2 (VEGFR-2) extracellular domains fused to the Fc portion of human IgG1.
	Summary of mode of action: Aflibercept acts as a soluble decoy receptor that binds vascular endothelial growth factor A (VEGF-A) and placental growth factor (PlGF) with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors. VEGF-A and PlGF are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases; VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF can synergise with VEGF-A in these processes and is also known to promote leucocyte infiltration and vascular inflammation.

Table Part I.1: Product(s) overview

	Important information about its composition: Aflibercept is produced in Chinese hamster ovary cells by recombinant DNA technology.
Hyperlink to the Product Information	Product Information
Indication(s) in the EEA	**Current:** OPUVIZ 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).
Dosage in the EEA	**Current:** Wet AMD The recommended dose for OPUVIZ is 2 mg aflibercept, equivalent to 0.05 mL. OPUVIZ treatment is initiated with one injection per month for three consecutive doses. The treatment interval is then extended to two months. Macular oedema secondary to RVO (branch RVO or central RVO) The recommended dose for OPUVIZ is 2 mg aflibercept equivalent to 0.05 mL. After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month. Monthly treatment continues until maximum visual acuity is achieved and/or there are no signs of disease activity. Three or more consecutive, monthly injections may be needed.

Table Part I.1: Product(s) overview

	DME The recommended dose for OPUVIZ is 2 mg aflibercept equivalent to 0.05 mL. OPUVIZ treatment is initiated with one injection per month for five consecutive doses, followed by one injection every two months. Myopic CNV The recommended dose for OPUVIZ is a single intravitreal injection of 2 mg aflibercept equivalent to 0.05 mL. Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists. Recurrences should be treated as a new manifestation of the disease.
Pharmaceutical form(s) and strengths	**Current:** Solution for injection in a vial 1 mL solution for injection contains 40 mg aflibercept. One vial contains an extractable volume of at least 0.1 mL, equivalent to at least 4 mg aflibercept. This provides a usable amount to deliver a single dose of 0.05 mL containing 2 mg aflibercept.
Is/will the product be subject to additional monitoring in the EU?	Yes

ATC = anatomical therapeutic chemical classification; DNA = deoxyribonucleic acid; EEA = European Economic Area; EU = European Union; Fc = fragment crystallisable; IgG1 = immunoglobulin G1; INN = international nonproprietary name.

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Based on the Guideline on good pharmacovigilance practices Module V – Risk management systems (Rev. 2), this module is not applicable for the medicinal product(s) seeking a marketing authorisation according to Article 10(4) of Directive 2001/83/EC, as amended.

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

A 4-week repeat-dose toxicity study was conducted in cynomolgus monkeys to demonstrate the similarity in toxicity profiles of OPUVIZ and the reference product EYLEA® (aflibercept). No safety pharmacology, genotoxicity, carcinogenicity, or reproductive and development toxicity studies were conducted fully in line with the European Medicines Agency (EMA) guideline EMA/CHMP/BMWP/403543/2010.

A detailed description of the non-clinical development programme for OPUVIZ is provided in the eCTD Module 2.4 (Non-clinical Overview).

Since the overall non-clinical programme for OPUVIZ showed that toxicity profile of OPUVIZ was similar to that of the reference product, the key non-clinical safety findings in Table SII.1 are based on the data collected for the reference product EYLEA.

Table SII.1: Key safety findings from non-clinical studies and relevance to human use

Key safety findings	Relevance to human usage
Impaired wound healing Impaired wound repair and healing was observed following repeated systemic administration of aflibercept in rabbits at all doses tested (0.3, 3, and 30 mg/kg) [1].	Impairment of wound healing is a known class effect of VEGF inhibitors [1, 2]. The relevance of these findings to OPUVIZ is considered low, considering the low systemic exposures, following intravitreal administration of 2 mg aflibercept.
Erosion and ulcerations of the respiratory epithelium Erosions and ulcerations of the respiratory epithelium in nasal turbinates were observed in the 8-month repeat dose toxicity study in cynomolgus monkeys treated with aflibercept intravitreally at systemic exposures in excess of the maximum human exposure [1]. These lesions were generally mild and reversible [3]. Based on the absence of effects on other tissues, these findings are considered more likely to the result from local exposure rather than systemic exposure to aflibercept [1, 3].	In cynomolgus monkey, the systemic exposure based on C_{max} and AUC for free aflibercept were approximately 200- and 700-fold higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg. Therefore, the relevance of these findings to human use is considered low.

Key safety findings	Relevance to human usage
Intraocular inflammation Inflammatory response characterised as inflammatory cells in the anterior chamber was noted following intravitreal injection of aflibercept in cynomolgus monkeys. This effect was seen predominately in aflibercept-treated eyes and was not dose or treatment duration related [1]. Of note, administration of the placebo alone also resulted in some inflammation [3]. The inflammatory response peaked at 2 days post injection and in all instances reversed within 3 weeks post dosing [1].	Intraocular inflammation is an important identified risk of aflibercept (refer to Part II: Module SVII).
Increased intraocular pressure (IOP) Reversible increase in ocular pressure was seen in either aflibercept or placebo-treated animals immediately after drug administration [1, 3]. This effect was considered due to the increase in vitreal volume following intravitreal injection since administration of a lower volume usually resulted in a much smaller immediate post dose increase in IOP [1].	Transient increase in IOP is an important identified risk of aflibercept (refer to Part II: Module SVII).
Genotoxicity and carcinogenicity No genotoxicity and carcinogenicity studies were conducted with aflibercept [1].	Aflibercept is not expected to be genotoxic or carcinogenic in humans.
Reproductive and developmental toxicity Embryo-foetal toxicity and foetal malformations were observed following IV administration of aflibercept (3 to 60 mg/kg) to pregnant rabbits in the embryo-foetal development study [1]. The combined early-embryonic and embryo-foetal development study conducted in pregnant rabbits with SC aflibercept administration (0.1 to 1 mg/kg) showed various foetal malformations at all doses [4].	At the 0.1 mg/kg dose, the systemic exposures based on cumulative AUC for free aflibercept were approximately 10-fold higher when compared to corresponding values observed in humans after an intravitreal dose of 2 mg. Embryo-foetotoxicity represents an important potential risk of aflibercept (refer to Part II: Module SVII).

Key safety findings	Relevance to human usage
Effects on male and female fertility Decreased sperm motility and increased spermatozoa morphological abnormalities in males and abrogation of ovarian function and follicular development in females during treatment with aflibercept, along with abrogation of normal menstruation were observed in 6-month study conducted in cynomolgus monkeys, following IV administration of 3 to 30 mg/kg aflibercept [1]. All effects were reversible after cessation of treatment.	Based on C_{max} and 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 exposure observed in humans after an intravitreal dose of 2 mg. Therefore, the relevance of these findings to human use is considered low.

AUC = area under the plasma concentration-time curve; C_{max} = maximum plasma concentration;
IV = intravenous; SC = subcutaneous.

Part II: Module SIII - Clinical trial exposure

The clinical development programme for OPUVIZ included a comparative Phase III study in subjects with neovascular AMD (Study SB15-3001). This randomised, double-masked, parallel group, multicentre study aimed to compare efficacy, safety, pharmacokinetics, and immunogenicity between OPUVIZ and the reference product EYLEA.

The duration of subject exposure to OPUVIZ and EYLEA is provided in Table SIII.1, while the subjects' demographic characteristics are detailed in Table SIII.2.

A detailed description of the clinical development programme for OPUVIZ is provided in the eCTD Module 2.5 (Clinical Overview) and Module 2.7.4 (Summary of Clinical Safety).

The safety profile of aflibercept and its positive benefit-risk balance is based solely on the data collected for the reference product EYLEA [5], taking into account data collected in Study SB15-3001.

Table SIII.1: Duration of exposure to investigational product (Safety Set 1)

Exposure	OPUVIZ (N = 224)	EYLEA (N = 224)		
		Overall (N = 224)	OPUVIZ (N = 111) [a]	EYLEA (N = 104) [a]
Duration of exposure to IP (days) up to Week 32				
n	224	224	-	-
Mean (SD)	221.7 (15.93)	221.8 (16.75)	-	-
Median	224.0	224.0	-	-
Min, max	28, 254	112, 259	-	-
Duration of exposure to IP (days) up to Week 56				
n	224	224	111	104
Mean (SD)	385.5 (37.11)	382.2 (47.17)	390.9 (12.31)	391.8 (6.94)
Median	392.0	392.0	392.0	392.0
Min, max	28, 424	112, 417	284, 413	343, 417
Duration of exposure to IP (days) up to Week 56, n (%)				
≥ 1	224 (100.0)	224 (100.0)	111 (100.0)	104 (100.0)
≥ 29	223 (99.6)	224 (100.0)	111 (100.0)	104 (100.0)
≥ 57	223 (99.6)	224 (100.0)	111 (100.0)	104 (100.0)
≥ 113	223 (99.6)	223 (99.6)	111 (100.0)	104 (100.0)
≥ 169	222 (99.1)	219 (97.8)	111 (100.0)	104 (100.0)
≥ 225	220 (98.2)	215 (96.0)	111 (100.0)	104 (100.0)
≥ 281	219 (97.8)	215 (96.0)	111 (100.0)	104 (100.0)
≥ 337	217 (96.9)	213 (95.1)	109 (98.2)	104 (100.0)

IP = investigational product; max = maximum; min = minimum; SD = standard deviation.
[a] Based on subjects who underwent re-randomisation at Week 32. Numbers may not add-up to Overall.

Table SIII.2: Demographic characteristics by treatment groups (Randomised Set)

Exposure	OPUVIZ (N = 224)	EYLEA (N = 225)		
		Overall (N = 225)	OPUVIZ (N = 111) [a]	EYLEA (N = 108) [a]
Age (years)				
n	224	225	111	108
Mean (SD)	73.7 (8.05)	74.3 (8.09)	74.7 (7.96)	73.8 (8.25)
Median	75.0	74.0	74.0	74.0
Min, max	50, 96	52, 93	52, 93	52, 93
Gender, n (%)				
Female	118 (52.7)	132 (58.7)	59 (53.2)	69 (63.9)
Male	106 (47.3)	93 (41.3)	52 (46.8)	39 (36.1)
Race, n (%)				
Asian	52 (23.2)	51 (22.7)	26 (23.4)	24 (22.2)
Black or African American	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.9)
White	170 (75.9)	172 (76.4)	84 (75.7)	83 (76.9)
Other	2 (0.9)	1 (0.4)	1 (0.9)	0 (0.0)
Ethnicity, n (%)				
Hispanic or Latino	1 (0.4)	1 (0.4)	1 (0.9)	0 (0.0)
Japanese	12 (5.4)	9 (4.0)	5 (4.5)	4 (3.7)
Mixed	6 (2.7)	5 (2.2)	2 (1.8)	3 (2.8)
Other	205 (91.5)	210 (93.3)	103 (92.8)	101 (93.5)

max = maximum; min = minimum; SD = standard deviation.
[a] Based on subjects who underwent re-randomisation at Week 32. Numbers may not add-up to Overall.

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

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The summary of important exclusion criteria presented in this section is based on the exclusion criteria selected for the comparative Phase III study SB15-3001 in subjects with neovascular AMD. However, any limitations of the clinical trial population are solely based on the data available for the reference product EYLEA [5].

Women of childbearing potential who were pregnant, planning to become pregnant, lactating, or not using adequate birth control, as specified in the protocol. For women of childbearing potential, a serum pregnancy test had to be negative at Screening.

Reason for exclusion	Aflibercept shown teratogenic effects and embryo-foetal toxicity in the non-clinical studies. Therefore, these criteria were selected to minimise potential risks to pregnancy and/or foetal development.
Is it considered to be included as missing information?	No
Rationale	Aflibercept should not be used during pregnancy and breast-feeding unless the potential benefit of therapy outweighs the potential risk to the foetus. Considering the target population demographics, including to a large extent elderly individuals, the use of aflibercept during pregnancy and breast-feeding does not represent an area of missing information.

Study eye: History of treatment involving macula such as macular laser photocoagulation, photodynamic therapy, transpupillary thermotherapy, radiation therapy, or any ocular treatment for neovascular AMD
Study eye: History of vitrectomy, scleral buckling (encircling), glaucoma filtration surgery, corneal transplantation, or pan-retinal photocoagulation
Study eye: Any other intraocular surgery (including cataract surgery or Yttrium Aluminium Garnet laser posterior capsulotomy in association with prior posterior chamber intraocular lens implantation) or periocular surgery within 90 days prior to randomisation, except for lid surgery, which was not allowed to take place within 30 days prior to randomisation.

Reason for exclusion	These criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants.
Is it considered to be included as missing information?	No
Rationale	The safety profile of aflibercept is not expected to differ in patients with a history of macula treatment. In patients undergoing intraocular surgery, aflibercept should be withheld within 28 days before and after the surgery.

Study eye: Uncontrolled ocular hypertension (defined as IOP ≥ 25 mmHg despite treatment with anti-glaucoma medication) at Screening

Reason for exclusion	These criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants, since intravitreal products are known to increase IOP.
Is it considered to be included as missing information?	No
Rationale	Intravitreal VEGF-inhibitors are associated with usually transient increases in IOP [6] and transient increase in IOP represents an important identified risk of aflibercept (refer to Part II: Module SVII). Aflibercept should not be administered to patients with poorly controlled glaucoma, whose IOP is ≥30 mmHg.

Uncontrolled systemic disease including but not limited to uncontrolled diabetes mellitus (in the opinion of the Investigator), uncontrolled systemic hypertension (systolic blood pressure [BP] ≥ 180 mmHg and/or diastolic BP ≥ 100 mmHg on optimal medical regimen), or uncontrolled atrial fibrillation (resting heart rate ≥ 110 beats per minute) at Screening

Reason for exclusion	These criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants.
Is it considered to be included as missing information?	No
Rationale	The safety profile of aflibercept is not expected to differ in these patient populations. However, special precaution during therapy with aflibercept is necessary.

Severe renal impairment with dialysis or a history of renal transplant

Reason for exclusion	These criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants.
Is it considered to be included as missing information?	No
Rationale	The safety profile of aflibercept is not expected to differ in patients with severe renal impairment. Available data do not suggest a need for a dose adjustment with aflibercept in these patients.

History of recurrent significant infections and/or current treatment for systemic infection

Reason for exclusion	These criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants.
Is it considered to be included as missing information?	No
Rationale	The safety profile of aflibercept is not expected to differ in patients with a history of recurrent infections or those treated for systemic infections during treatment with aflibercept.

Either eye: Active or suspected ocular and periocular infection at Screening or at randomisation (e.g., infectious blepharitis, infectious conjunctivitis, infection in eyelid)
Either eye: Active intraocular inflammation including scleritis at Screening or at randomisation
Either eye: History of idiopathic or autoimmune-associated uveitis

Reason for exclusion	These criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants.
Is it considered to be included as missing information?	No
Rationale	Active or suspected ocular and periocular infection and active severe intraocular inflammation represent contraindications for use of aflibercept.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions, such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment	Not included in the clinical development programme or not specifically studied.
Population with relevant different ethnic origin	Refer to Table SIII.2.
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Elderly population	Subjects ≥ 65 years of age were included in the clinical development programme (refer to Table SIII.2). The mean age of subjects exposed to OPUVIZ was 73.7 years (range: 50-96).

Part II: Module SV - Post-authorisation experience

OPUVIZ has not yet been approved for marketing in any country

SV.1 Post-authorization exposure

Not applicable.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

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

Potential for misuse for illegal purposes

The potential for misuse for illegal purposes is considered negligible, given the mechanism of action 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

There are currently no risks considered as not important for inclusion in the list of safety concerns in respect to this RMP.

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

The safety concerns in the RMP for a biosimilar product OPUVIZ are aligned with the safety concerns for the reference product EYLEA [7], taking into account findings from the comparative study SB15-3001 and potential unique characteristics of the OPUVIZ medicinal product.

Important identified risk(s):

- **Endophthalmitis (likely infectious origin)**

Risk-benefit impact:

Endophthalmitis is a potentially sight-threatening condition associated with intravitreal products. If not appropriately treated in a timely manner, endophthalmitis can lead to severe vision loss or blindness. Considering the characteristics of the target population, the risk minimisation measures in place, and its infrequent occurrence in clinical practice, the impact of this risk on the benefit-risk balance of aflibercept is considered acceptable.

- **Intraocular inflammation**

Risk-benefit impact:

Intraocular inflammation is a relatively uncommon adverse effect of the therapy, with a vision-altering potential and marked impact on patient's quality of life. Considering the reversibility of intraocular inflammation in a vast majority of affected patients and the risk minimisation measures in place, the benefits of aflibercept therapy outweigh this risk.

- **Transient intraocular pressure increase**

Risk-benefit impact:

Mostly transient, short-term, mild to moderate IOP elevations have been associated with aflibercept intravitreal therapy that spontaneously resolve with or without IOP-lowering medication. However, severe IOP elevations requiring surgery or chronic IOP elevations have also been described, albeit infrequently. Considering the benefits of aflibercept therapy and risk minimisation measures in place, the impact of this risk on the benefit-risk balance of aflibercept is acceptable.

- **Retinal pigment epithelial tears**

Risk-benefit impact:

Retinal pigment epithelial tears represent a serious but infrequent adverse effect of aflibercept therapy in susceptible patients, with potentially negative impact on patient's visual acuity. Considering the benefits of aflibercept therapy and risk minimisation measures in place, the impact of this risk on the benefit-risk balance of aflibercept is acceptable.

- **Cataract (especially of traumatic origin)**

Risk-benefit impact:

Traumatic cataract is an infrequent, albeit serious adverse effect associated with intravitreal injections, irrespective of the mode of action of the drug substance. This adverse effect is preventable by proper injections techniques. As such, the benefits of aflibercept treatment fully outweigh this risk.

Important potential risk(s):

- **Medication errors**

Risk-benefit impact:

The impact of medication errors on benefit-risk balance of aflibercept is acceptable, considering the nature of the expected undesirable clinical outcomes and risk minimisation measures in place.

- **Off-label use and misuse**

Risk-benefit impact:

The impact of this risk on the benefit-risk balance of aflibercept is acceptable, considering the broad indications for use in the EU and the favourable safety characteristics of aflibercept in different indications.

- **Embryo-foetotoxicity**

Risk-benefit impact:

Aflibercept is an anti-angiogenic substance that showed teratogenic and embryotoxic effects in animal models, following intravenous administration. Considering the characteristics of the target population of aflibercept, intravitreal administration minimising systemic exposure to the drug, and risk minimisation measures in place, the impact of this risk on the benefit-risk balance of aflibercept is acceptable.

Missing information:

None

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

Not applicable.

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

SVII.3.1 Presentation of important identified risks and important potential risks

Important identified risk 1: Endophthalmitis (likely infectious origin)

Potential mechanisms:

Endophthalmitis associated with the use of intravitreal products usually results from the patient's own conjunctival flora. Contamination of sterilised instruments and supplies needed for the procedure can also introduce causative agents into the eye.

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of aflibercept as reflected in the Product Information and the summary of safety concerns for the reference product EYLEA [5, 7].

Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency of endophthalmitis (culture positive or negative) in association with aflibercept is 'uncommon' (i.e. ≥1 in 1,000 to <1 in 100), based on the overall experience with aflibercept from eight Phase III clinical studies, encompassing data from 3,102 patients with wet AMD, RVO, DME, and myopic CNV, and the post-marketing experience [5].

No event of (suspected) intraocular infection, including endophthalmitis, occurred in the comparative Phase III study SB15-3001.

Endophthalmitis is the most serious, albeit infrequent, complication of intravitreal injections of VEGF inhibitors, as endophthalmitis can cause blindness, if not appropriately treated in a timely manner [8].

There is an overlap in time to presentation and symptoms of infectious endophthalmitis with intraocular inflammation and it is crucial to differentiate between these two conditions since management and prognosis differ.

Literature shows that infectious endophthalmitis classically presents after 3 to 5 days post injection [9]. The predominant clinical presentations differentiating endophthalmitis from intraocular inflammation are severe pain (notably missing in about one quarter of patients), conjunctival injection, and hypopyon [9].

The outcome of endophthalmitis caused by infectious agents often depends on the organism causing the infection. Based on the available literature, the majority of infectious endophthalmitis are caused by coagulase-negative *Staphylococcus* species, which are usually associated with good outcomes following rapid treatment, unlike endophthalmitis caused by *Streptococcus* species [10].

Risk factors and risk groups:

Improper aseptic techniques used during the procedure represent a general risk factor for endophthalmitis. No specific groups at risk have been established for aflibercept.

Preventability:

Proper aseptic injection techniques must always be used when administering OPUVIZ. Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. In general, adequate anaesthesia and asepsis, including topical broad-spectrum microbicide (e.g. povidone iodine), applied to the periocular skin, eyelid, and ocular surface, have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended.

Patients should be monitored during the week following the injection to permit early treatment if an infection occurs. They should be instructed to report any symptoms suggestive of endophthalmitis (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay.

The vial formulation is for single use in one eye only.

Part V.2 details additional risk minimisation measures in place for this risk.

Impact on the risk-benefit balance of the product:

Endophthalmitis is a potentially sight-threatening condition associated with intravitreal products. If not appropriately treated in a timely manner, endophthalmitis can lead to severe vision loss or blindness. Considering the characteristics of the target population, the risk minimisation measures in place and the infrequent occurrence in clinical practice, the impact of this risk on the benefit-risk balance of aflibercept is considered acceptable.

Public health impact:

No impact on public health is expected.

Important identified risk 2: Intraocular inflammation

Potential mechanisms:

Sterile intraocular inflammation is a known complication of therapeutic intravitreal injections. The mechanism for development of aflibercept-associated intraocular inflammation seems multifactorial but has not yet been fully elucidated. The hypothesised causes include patient-specific factors (including a history of uveitis or immunologic response to the product), contamination, improper storage and handling, or impurities introduced from the vehicle [9].

Some cases of intraocular inflammation associated with aflibercept were attributed to certain batches of syringes included in specific lots of EYLEA kits [9].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of aflibercept as reflected in the Product Information and the summary of safety concerns for the reference product EYLEA [5, 7].

Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency of intraocular inflammation in association with aflibercept, including iritis, iridocyclitis, and uveitis, is 'uncommon' (i.e. ≥1 in 1,000 to <1 in 100), while the frequency of vitritis is 'rare' (≥1 in 10,000 to <1 in 1,000), based on the overall experience with aflibercept from eight Phase III clinical studies, encompassing data from 3,102 patients with wet AMD, RVO, DME, and myopic CNV, and the post-marketing experience [5].

A single event of iridocyclitis in the study eye occurred in 1 (0.2%) patient receiving EYLEA/OPUVIZ in the overall study period of the comparative Phase III study SB15-3001, which occurred in a patient receiving EYLEA prior to re-randomisation.

Multiple post-marketing studies focused on the aflibercept-associated intraocular inflammation with the aim to identify the nature of this adverse effect [9, 11-14].

Sterile intraocular inflammation tends to present sooner than infectious endophthalmitis, usually within 2 to 3 days (range 0 to 30 days), but there is certain overlap in time to presentation [9, 11]. Common examination finding included vitritis and anterior chamber reaction, usually combined [9, 11].

The symptoms of intraocular inflammation from a large post-marketing analysis of cases reported to the American Society of Retina Specialists' Research and Safety in Therapeutics Committee included blurry vision (93%), floaters (60%), pain (44%), and photophobia (19%) [9]. Similar findings were reported in other analysis of post-marketing cases [11].

Severe pain affected only 6% of patients with suspected intraocular inflammation and only a minority of patients presented with conjunctival injection (about 10% of patients as opposite to 82% reported in association with infectious endophthalmitis) [9].

Majority of patients were treated with topical steroids, supplemented by oral steroids in minority of affected patients, or observation alone [9, 11]

Intraocular inflammation had resolved with the mean time to resolution of 34 days (range 7 to 105 days) and the majority of patients described in the literature returned to baseline visual acuity (only about 15% of patients had lost two lines or more of final visual acuity) [9, 11].

There did not seem to be any significant differences in visual outcome for age, gender, lens status, other symptoms, examination findings, or time to resolution [9]. Worse outcome was noted in association with more acute and more severe presentation of intraocular inflammation. Patients above 80 years of age also experienced worse outcomes [9, 11].

Risk factors and risk groups:

Considering the unknown mechanism for this effect, general risk factors have not yet been established. As literature showed, some cases reported in aflibercept in the post-marketing phase were attributed to batches of syringes used for intravitreal injection included in specific lots of EYLEA kits [9].

Preventability:

Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections.

Part V.2 details additional risk minimisation measures in place for this risk.

Impact on the risk-benefit balance of the product:

Intraocular inflammation is a relatively uncommon adverse effect of the therapy, with a vision-altering potential and marked impact on patient's quality of life. Considering the reversibility of intraocular inflammation in a vast majority of affected patients and the risk minimisation measures in place, the benefits of aflibercept therapy outweigh this risk.

Public health impact:

No impact on public health is expected.

Important identified risk 3: Transient intraocular pressure increase

Potential mechanisms:

Acute elevations in IOP stem directly from the acute increase of volume in a relatively closed space, associated with intravitreal injections [6].

The mechanism for persistent elevations in IOP following VEGF inhibitor intravitreal therapy is less understood and several hypotheses have been proposed, including reduced aqueous outflow, repeated and ongoing injury to the trabecular meshwork from the repeated injection of high volume, alterations in levels of trabecular meshwork vasodilating modulators such as nitric oxide, toxic effects of drugs or drug delivery, or inflammatory damage [6].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of aflibercept as reflected in the Product Information and the summary of safety concerns for the reference product EYLEA [5, 7].

Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency of IOP increased in association with aflibercept is 'common' (i.e. ≥1 in 100 to <1 in 10), based on the overall experience with aflibercept from eight Phase III clinical studies, encompassing data from 3,102 patients with wet AMD, RVO, DME, and myopic CNV, and the post-marketing experience [5].

Three events of IOP elevation occurred during the overall period in the Phase III comparative study SB15-3001, 2 events associated with IOP elevations were reported in 2 patients (0.9%) in the OPUVIZ/OPUVIZ treatment group in the transition period and 1 patient (0.4%) in the EYLEA treatment group in the main period. The event of glaucoma was mild in intensity and considered related to OPUVIZ and the event of IOP increased was mild in intensity and considered not related to OPUVIZ in the OPUVIZ/OPUVIZ treatment group. For the patient in

the EYLEA/EYLEA treatment group, the event of glaucoma was moderate in intensity and considered not related to EYLEA.

Elevations in IOP following intravitreal injection of VEGF inhibitors are usually transient, well tolerated, and fully reversible within a week [6]. Acute spikes in IOP are often accompanied by pain and acute loss of vision [6].

Most often, the elevations in IOP are manageable with topical monotherapy. In more severe cases, combination of medicinal products may be required, as well as selective laser trabeculoplasty. However, the need for filtering surgery has be reported, albeit rarely [15].

Several case reports described acute angle-closure glaucoma temporally related to intravitreal injection, requiring anti-glaucoma treatment [6]. Chronic, sustained elevations in IOP of previously normotensive eyes, distinct from the short-term acute ocular hypertension, were also reported in association with VEGF therapy [15, 16].

As such, three categories of IOP elevations following intravitreal injections were proposed: early (or acute) causing rise within minutes post injection, intermediate causing rise lasting several hours, and chronic lasting several months [6].

Retrospective analysis of data from the registry 'The Fight Retinal Blindness!', including data from 395 bevacizumab-, 1,138 aflibercept-, and 1,896 ranibizumab-treated eyes with at least 3 injections and 12-month follow-up, showed that the mean IOP did not change from baseline to 12 and 24 months in eyes receiving VEGF inhibitors and clinically significant IOP elevations (defined as increase of at least 6 mmHg from baseline and resulting in an IOP of >21 mmHg in a single event) occurred in a small proportion of eyes (5.6% [193 eyes] at 12 months and 8.8% [186 eyes] at 24 months). The rates of clinically significant elevated IOP at 12 and 24 months were 2.4% and 3.9% in the aflibercept group, 5.2% and 9.7% in the bevacizumab group, and 6.4% and 9.4% in the ranibizumab group, respectively [17].

Risk factors and risk groups:

Specific risk factors and risk groups have not yet been established for aflibercept.

Several studies suggest that eyes with a history of glaucoma are at a higher risk for IOP elevation following intravitreal injection with VEGF inhibitors [6]. Special precaution is needed in patients with poorly controlled glaucoma and OPUVIZ should not be administered to patients, whose IOP is ≥30 mmHg.

In addition to history of glaucoma, other potential risk factors proposed in the literature include the type of retinal pathology, volume of injected medication, and intraocular fluid dynamics [6].

The risk factors identified for the chronic, sustained elevations in IOP include the total number of injections and a greater frequency of administration [18].

Preventability:

Based on the literature, pre-treatment with topical IOP-lowering agents should be routinely considered before intravitreal injections, particularly in eyes with glaucoma or known history of sustained IOP elevation, in whom the chronic effects are not yet known [6].

Immediately following the intravitreal injection, patients should be monitored for elevation in IOP. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available.

Part V.2 details additional risk minimisation measures in place for this risk.

Impact on the risk-benefit balance of the product:

Mostly transient, short-term, mild to moderate IOP elevations have been associated with aflibercept intravitreal therapy that spontaneously resolve with or without IOP-lowering medication. However, severe IOP elevations requiring surgery or chronic IOP have also been described, albeit infrequently. Considering the benefits of aflibercept therapy and the risk minimisation measures in place, the impact of this risk on the benefit-risk balance of aflibercept is acceptable.

Public health impact:

No impact on public health is expected.

Important identified risk 4: Retinal pigment epithelial tears

Potential mechanisms:

The cause of retinal pigment epithelial tears has not yet been fully elucidated and appears multifactorial [19, 20].

Retinal pigment epithelium tears are known to occur as a natural result in the course of a retinal pigment epithelial detachment of the underlying CNV, retinal angiomatous proliferation, or polypoidal choroidal vasculopathy [21].

Several mechanisms have been proposed, including the role of subretinal fluid applying hydrostatic pressure to the retinal pigment epithelium, causing it to stretch, and contraction of the choroidal neovascular membrane adding tractional forces to the already delicate retinal pigment epithelium layer [20].

It has been hypothesised that intravitreal injections with VEGF inhibitors, including aflibercept, create an extra contraction force in a pigment epithelial detachment at risk, triggering the retinal pigment epithelial tear. VEGFs inhibition creates an imbalance favouring connective tissue growth factor, which favours inflammatory and fibrous elements with contractile capacity, in line with recent histopathological studies [19].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of aflibercept as reflected in the Product Information and the summary of safety concerns for the reference product EYLEA [5, 7].

Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency of retinal pigment epithelial tears in association with aflibercept is ‘common’ (i.e. ≥1 in 100 to <1 in 10), based on the overall experience with aflibercept from eight Phase III clinical studies, encompassing data from 3,102 patients with wet AMD, RVO, DME, and myopic CNV, and the post-marketing experience [5]. This event was only observed in wet AMD studies.

During the Phase III comparative study SB15-3001, 2 events of retinal pigment epithelial tear were reported in 2 patients (0.9%) in the OPUVIZ treatment group (1 [0.4%] patient in the OPUVIZ treatment group in the main period and 1 [0.5%] patient in the OPUVIZ/OPUVIZ treatment group in the transition period). One of the events was mild in intensity and considered not related to OPUVIZ or the intravitreal injection procedure. The other event was moderate in intensity and considered related to OPUVIZ.

VEGF inhibitor-associated retinal pigment epithelium tears often develop shortly after the first to third injection and the literature reports the average number of injections before the development of an retinal pigment epithelium tear was 1.3 and median time between last injection and diagnosis was 4 weeks [22, 23].

Retinal pigment epithelium tears frequently lead to significant loss of visual acuity [21].

Risk factors and risk groups:

Patients with wet AMD represent a known risk group for the spontaneous development of retinal pigment epithelial tears. Therefore, this population is at risk of retinal pigment epithelial tears development associated with VEGF inhibitors.

The risk factors described in the literature for developing retinal pigment epithelial tears at baseline or during anti-VEGF therapy in patients with vascularised pigment epithelial detachment with wet AMD include [19]:

- retinal pigment epithelial detachment height above 400 µm
- presence of microtears
- presence of a subretinal cleft
- fibrovascular retinal pigment epithelial detachment
- history of photodynamic therapy.

A high-risk patient for development of retinal pigment epithelium tears is defined as showing one or more of the risk factors at the beginning or during the course of an anti-VEGF treatment [21].

It has been hypothesised that there may be a greater risk of retinal pigment epithelial tear associated with aflibercept than with ranibizumab or bevacizumab, as aflibercept has a stronger bond to VEGF than ranibizumab, but further studies are required to corroborate this hypothesis [19].

Preventability:

When starting an aflibercept treatment regimen, caution should be exercised as retinal pigment epithelial tears may be difficult to be prevented due to the background disease progression. Therefore, patients with neovascular (wet) AMD with larger pigment epithelial detachments, which is the risk factor of retinal pigment epithelial tears, should be notified in advance of the above side effects and the possibility of sudden and severe vision loss after injection. Some literatures suggests that when high risk factors are identified, VEFG inhibitors should be discontinued with regular follow up until the risk factors have declined.

Part V.2 details additional risk minimisation measures in place for this risk.

Impact on the risk-benefit balance of the product:

Retinal pigment epithelial tears represent a serious but infrequent adverse effect of aflibercept therapy in susceptible patients, with potentially negative impact on patient's visual acuity. Considering the benefits of aflibercept therapy and risk minimisation measures in place, the impact of this risk on the benefit-risk balance of aflibercept is acceptable.

Public health impact:

No impact on public health is expected.

Important identified risk 5: Cataract (especially of traumatic origin)

Potential mechanisms:

Cataracts (especially of traumatic origin) following intravitreal injections are associated with needle-induced trauma to the lens capsule, most often caused by improper manipulation during procedure.

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of aflibercept as reflected in the Product Information and the summary of safety concerns for the reference product EYLEA [5, 7].

Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency of cataract (cataract, cataract cortical, cataract nuclear, and cataract subcapsular) in association with aflibercept is 'common' (i.e. ≥1 in 100 to <1 in 10), while the frequency of cataract traumatic is 'rare' (≥1 in 10,000 to <1 in 1,000), based on the overall experience with aflibercept from eight Phase III clinical studies, encompassing data from 3,102 patients with wet AMD, RVO, DME, and myopic CNV, and the post-marketing experience [5].

In the overall period of the Phase III comparative study SB15-3001, events related to cataract are shown in Table SVII.1, and no event of traumatic cataract occurred in this study. Similar data were collected for the overall period in the fellow eye.

Table SVII.1: Number and frequency of cataract TEAEs in the study eye from the Phase III study SB15-3001 (Safety Set 1)

MedDRA PT	OPUVIZ N = 224	EYLEA		
		Total N = 224	OPUVIZ N = 111[a]	EYLEA N = 104[a]
	n (%)	n (%)	n (%)	n (%)
Cataract	4 (1.8)	5 (2.2)	3 (2.7)	2 (1.9)
Cataract cortical	0 (0.0)	1 (0.4)	0 (0.0)	1 (1.0)
Cataract nuclear	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cataract subcapsular	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Traumatic cataract	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	**5 (2.2)**	**6 (2.7)**	**3 (2.7)**	**3 (2.9)**

MedDRA = Medical Dictionary for Regulatory Authorities; PT = preferred term; TEAE = treatment-emergent adverse event.
[a] Based on patients who underwent re-randomisation at Week 32. Numbers may not add-up to Overall.

The occurrence of traumatic cataract, infrequently associated with VEGF inhibitors, is independent of the drug administered (unlike steroid-induced cataracts).

The majority of traumatic cataracts are visually significant and require surgery.

Risk factors and risk groups:

The risk factors and groups have not yet been established for aflibercept.

Preventability:

OPUVIZ must only be administered by qualified physician experienced with intravitreal injections, following proper injection techniques.

Part V.2 details additional risk minimisation measures in place for this risk.

Impact on the risk-benefit balance of the product:

Traumatic cataract is an infrequent, albeit serious adverse effect associated with intravitreal injections, irrespective of the mode of action. This adverse effect is preventable by utilising proper injections techniques. As such, the benefits of aflibercept treatment fully outweigh this risk.

Public health impact:

No impact on public health is expected.

Important potential risk 1: Medication errors

Potential mechanisms:

Aflibercept is provided in a vial that contains an excess volume, enabling to administer the intended volume of 0.05 mL, containing the recommended dose of 2 mg aflibercept.

This excess volume must be expelled before injecting the recommended dose. Injecting the entire volume of the vial could result in overdose.

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of aflibercept as reflected in the Product Information and the summary of safety concerns for the reference product EYLEA [5, 7].

Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

In clinical trials with aflibercept, doses of up to 4 mg in monthly intervals have been used and isolated cases of overdoses with 8 mg occurred.

No overdose occurred in the comparative in the Phase III comparative study SB15-3001.

Administration of a full volume available in vial may result in aflibercept overdose. Overdosing with increased injection volume may increase IOP. Therefore, in case of overdose, IOP should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

Risk factors and risk groups:

The risk groups or risk factor for undesirable outcomes associated with medication errors have not yet been established for aflibercept.

Preventability:

OPUVIZ must only be administered by qualified physician experienced with intravitreal injections, following proper injection techniques.

Part V.2 details additional risk minimisation measures in place for this risk.

Impact on the risk-benefit balance of the product:

The impact of medication errors on the benefit-risk balance of aflibercept is acceptable, considering the nature of expected undesirable clinical outcomes and risk minimisation measures in place.

Public health impact:

No impact on public health is expected.

Important potential risk 2: Off-label use and misuse

Potential mechanisms:

Not applicable.

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of aflibercept as reflected in the Product Information and the summary of safety concerns for the reference product EYLEA [5, 7].

Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

As any other medicinal product, OPUVIZ can be used for a medical purpose not in accordance with the terms of the marketing authorisation.

The experience with the use of OPUVIZ in off-label use situations is limited.

Risk factors and risk groups:

The specific risk factors or groups at risk have not yet been established for aflibercept.

Preventability:

OPUVIZ should be used in line with the terms of marketing authorisation, including approved indication for use or recommended posology.

Part V.2 details additional risk minimisation measures in place for this risk.

Impact on the risk-benefit balance of the product:

The impact of this risk on the benefit-risk characteristics of aflibercept is acceptable, considering the broad indications for use in the EU and the favourable safety characteristics of aflibercept in different indications.

Public health impact:

No impact on public health is expected.

Important potential risk 3: Embryo-foetotoxicity

Potential mechanisms:

Aflibercept has an anti-angiogenic activity. Therefore, its teratogenic/embryotoxic effects stem directly from the mode of action since angiogenesis plays a critical role in foetal development.

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of aflibercept as reflected in the Product Information and the summary of safety concerns for the reference product EYLEA [5, 7].

Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

Adequate and well-controlled studies with aflibercept have not been conducted in pregnant women and there are no data on the use of aflibercept during pregnancy.

No teratogenic/embryotoxic effects have been observed to date, following intravitreal administration of aflibercept.

Risk factors and risk groups:

Women of childbearing potential represent a general risk group for these effects. Aflibercept should not be used during the whole pregnancy, however, the first trimester seems to be the most susceptible period of pregnancy to the adverse effects associated with aflibercept.

Preventability:

Although the systemic exposure after ocular administration is low, OPUVIZ should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.

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

Part V.2 details additional risk minimisation measures in place for this risk.

Impact on the risk-benefit balance of the product:

Aflibercept is an anti-angiogenic substance that showed teratogenic and embryotoxic effects in animal models, following intravenous administration. Considering the characteristics of target population of aflibercept, intravitreal administration minimising systemic exposure to the drug and risk minimisation measures in place, the impact of this risk on benefit-risk balance of aflibercept is acceptable.

Public health impact:

No impact on public health is expected.

SVII.3.2 Presentation of the missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

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 risk	Medication errors Off-label use and misuse Embryo-foetotoxicity
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:

- **Specific adverse reaction follow-up questionnaires for endophthalmitis (likely infectious origin) and intraocular inflammation**

Any post-marketing reports suspected of intraocular infection and intraocular inflammation will be followed-up with the use of a targeted questionnaire.

This questionnaire is designed to obtain structured information on the reported suspected intraocular infection and intraocular inflammation to deepen the understanding of this risk associated with aflibercept.

This form aims to collect detailed information about the patient, concerned medicinal product, patient's history, relevant laboratory findings (bacteriology, serology, biopsy), clinical presentation of the event, and information on the treatment.

The questionnaire is provided in Annex 4.

III.2 Additional pharmacovigilance activities

There are no ongoing or planned additional pharmacovigilance activities.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

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

Risk Minimisation Plan

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) PL section 2 (What you need to know before you are given Opuviz) PL 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), a comprehensive description of the injection procedure (including short term follow-up) is provided in order to ensure high-quality standard of the intervention. • SmPC Section 4.2 (Posology and method of administration) and PL section 2 (What you need to know before you are given Opuviz): Suggestive symptoms of endophthalmitis are mentioned. • "Active or suspected ocular or periocular infection" is listed in SmPC Section 4.3 (Contraindications) and PL section 2 (What you need to know before you are given Opuviz). • SmPC Section 4.4 (Special warnings and precautions for use): Instructions for aseptic injection techniques, monitoring and instructions of patients are mentioned. • PL section 2 (What you need to know before you are given Opuviz): Description of symptoms potentially indicative of endophthalmitis is given. Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription.

Safety concern	Routine risk minimisation activities
	Aflibercept 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) PL section 2 (What you need to know before you are given Opuviz) PL 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 in order to ensure high-quality standard of the intervention. • "active or suspected ocular or periocular infection" and "active severe intraocular inflammation" are listed in SmPC Section 4.3 (Contraindications) and PL section 2 (What you need to know before you are given Opuviz). • 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 Eylea is mentioned (see Section 4.8). Monitoring of symptoms is advised. • Package Leaflet section 2 (What you need to know before you are given Opuviz): Description, monitoring and early treatment of symptoms are mentioned. • Package Leaflet section 3 (How you will be given Opuviz): Description on pre-injection use of disinfectant for cleaning measures provided. Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections

Safety concern	Routine risk minimisation activities
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) PL section 2 (What you need to know before you are given Opuviz) **PL 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 in order to ensure high-quality standard of the intervention. • SmPC Section 4.2 (Method of administration): Appropriate monitoring for elevation in intraocular pressure is mentioned. Special precaution in patients with poorly controlled glaucoma is mentioned. • SmPC Section 4.4 (Special warnings and precautions for use): Excess volume from the 2 mg aflibercept vial must be discarded prior to administration. • Package Leaflet section 2 (What you need to know before you are given Opuviz): Injections with aflibercept may cause an increase in eye pressure. • SmPC Section 4.9 (Overdose): Effect of overdosing, monitoring and treatment of intraocular pressure by the physician are mentioned. Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections
Retinal pigment epithelial tears	Routine risk communication

Safety concern	Routine risk minimisation activities
	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 Opuviz) **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 aflibercept therapy in patients with this risk factor. • PL section 2 (What you need to know before you are given Opuviz): 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: Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections
Cataract (especially of traumatic origin)	Routine risk communication SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) PL section 2 (What you need to know before you are given Opuviz) **PL 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), a comprehensive description of the injection procedure (including

Safety concern	Routine risk minimisation activities
	short- term follow-up) is provided in order to ensure high-quality standard of the intervention. • SmPC Section 4.4 (Special warnings and precautions for use): Instructions for aseptic injection techniques, monitoring and instructions for patients are mentioned. • PL section 2 (What you need to know before you are given Opuviz): Description, monitoring and early treatment of symptoms are mentioned. • PL section 3 (How you will be given Opuviz): "Before the injection your doctor will use a disinfectant eyewash to clean your eye carefully to prevent infection." Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription. Aflibercept 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) PL section 1 (What Opuviz is and what it is used for) **PL section 3 (How you will be given Opuviz)** Routine risk minimisation activities recommending specific clinical measures to address the risk: • In SmPC Section 4.2 (Posology and methods of administration) and PL section 'information intended for HCPs only', a detailed verbal instruction is provided for the handling of vial in order to minimize 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: Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections
Off-label use and misuse	Routine risk communication

Safety concern	Routine risk minimisation activities
	SmPC section 4.1 (Therapeutic indications) SmPC section 4.2 (Posology and method of administration) PL section 1 (What Opuviz is and what it is used for) PL section 2 (What you need to know before you are given Opuviz) PL section 3 (How you will be given Opuviz) Routine risk minimisation activities recommending specific clinical measures to address the risk: • In SmPC Section 4.2 (Posology and method of administration) and PL section 2 (What you need to know before you are given Opuviz), the following text is provided to prevent off-label use in paediatric population: "The safety and efficacy of aflibercept have not been established in children and adolescents. There is no relevant use of aflibercept in the paediatric population for the indications of wet AMD, CRVO, BRVO, DME and myopic CNV." • Contraindications are listed in SmPC Section 4.3 (Contraindications) and PL section 2 (What you need to know before you are given Opuviz) • Conditions in which treatment should be withheld/discontinued/not recommended are included in the SmPC section 4.4 (special warnings and precautions for use) and PL section 2 (What you need to know before you are given Opuviz) • Conditions of use in pregnancy and breastfeeding are included in the SmPC section 4.6 and PL section 2 (What you need to know before you are given Opuviz) Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections
Embryo-foetotoxicity	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) PL section 2 (What you need to know before you are given Opuviz) Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety concern	Routine risk minimisation activities
	• SmPC Section 4.4 (Special warnings and precautions for use) and Package Leaflet section 2 (What you need to know before you are given Opuviz: Instructions for pregnancy and women of childbearing potential are mentioned. • SmPC Section 4.6 (Fertility, pregnancy and lactation): Instructions for pregnancy and women of childbearing potential are mentioned. • PL section 2 (What you need to know before you are given Opuviz): Instructions for pregnancy and women of childbearing potential are mentioned. Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections

PL = Package Leaflet; SmPC = Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

Educational materials

- **Prescriber's guide and video**

Objectives:

To instruct and educate the treating physicians about the indications and contraindication for use, safety profile of aflibercept, including the need for patients' monitoring, and on the appropriate techniques for intravitreal administration of OPUVIZ and other key instructions for use. Also to raise physicians' awareness on important identified and potential risks, off-label use, medication error, treatment of women of child-bearing potential, and the need for appropriate contraception in women of childbearing potential.

Rationale for the additional risk minimisation activity:

OPUVIZ is a product intended for intravitreal administration. These educational materials are designed to provide additional information on safe use of OPUVIZ.

- List of addressed safety concerns:

  Endophthalmitis (likely infectious origin)

  Intraocular inflammation

  Transient intraocular pressure increase

  Retinal pigment epithelial tears

  Cataract (especially of traumatic origin)

  Medication errors

  Off-label use and misuse

  Embryo-foetotoxicity

Target audience and planned distribution path:

The target audience represent prescribing physicians experienced in administering intravitreal injections.

The prescriber's educational materials will be distributed in accordance with the local distribution plan approved by the respective national competent authority.

Plan to evaluate the effectiveness of the interventions and criteria for success:

Not applicable.

- **Patient's guide (including its audio version) for wet AMD, myopic CNV, DME, and branch and central RVO**

Objectives:

To inform patients about the safety profile of aflibercept, including key signs and symptoms of serious adverse effects, and to instruct patients to seek immediate medical attention if any of these signs or symptoms occur. Also to raise patients' awareness on important identified and potential risks, off-label use, treatment of women of child-bearing potential, and the need for appropriate contraception in women of childbearing potential.

Rationale for the additional risk minimisation activity:

OPUVIZ is a product intended for intravitreal administration. These educational materials are designed to provide additional information on safe use of OPUVIZ.

- List of addressed safety concerns:

  Endophthalmitis (likely infectious origin)

  Intraocular inflammation

  Transient intraocular pressure increase

  Retinal pigment epithelial tears

  Cataract (especially of traumatic origin)

  Medication errors

  Off-label use and misuse

  Embryo-foetotoxicity

Target audience and planned distribution path:

The target audience is represented by patients with wet AMD, myopic CNV, DME, or branch or central RVO prescribed with OPUVIZ.

Plan to evaluate the effectiveness of the interventions and criteria for success:

Not applicable.

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 SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 2, 3, and 4 Patients should be monitored a week following injection per the SmPC section 4.4. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay per the SmPC section 4.2 and 4.4. Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimisation Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Targeted follow-up questionnaire Additional pharmacovigilance activities None
Intraocular inflammation	Routine risk minimisation SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 2, 3, and 4 Patients should be monitored a week following injection per the SmPC section 4.4. Patients should be instructed to report any symptoms of intraocular	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Targeted follow-up questionnaire Additional pharmacovigilance activities None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	inflammation per the SmPC section 4.4. Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections <u>Additional risk minimisation</u> Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD	
Transient intraocular pressure increase	<u>Routine risk minimisation</u> SmPC sections 4.2, 4.4, 4.8, and 4.9 PL sections 2 and 4 Patients should be monitored immediately following the injection per the SmPC section 4.2. Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections <u>Additional risk minimisation</u> Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection</u> None <u>Additional pharmacovigilance activities</u> None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	(myopic), DME, and wet AMD	
Retinal pigment epithelial tears	Routine risk minimisation SmPC sections 4.4 and 4.8 PL sections 2 and 4 Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimisation Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Cataract (especially of traumatic origin)	Routine risk minimisation SmPC sections 4.2, 4.4, and 4.8 PL sections 2, 3, and 4 Subject to restricted medical prescription Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimisation Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	(branch and central), CNV (myopic), DME, and wet AMD	
Medication errors	Routine risk minimisation SmPC sections 4.2, 4.9, and 6.6 PL sections 1 and 3 Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimisation Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Off-label use and misuse	Routine risk minimisation SmPC sections 4.1, 4.2, 4.3, 4.4, and 4.6 PL sections 1, 2, and 3 Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimisation Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	(branch and central), CNV (myopic), DME, and wet AMD	
Embryo-foetotoxicity	Routine risk minimisation SmPC sections 4.4, 4.6, and 5.3 PL section 2 Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept as per the SmPC section 4.4 and 4.6. Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimisation Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None

AMD = age-related macular degeneration; CNV = choroidal neovascularisation; DME = diabetic macular oedema; PL = Package Leaflet; RVO = retinal vein occlusion; SmPC = Summary of Product Characteristics.

Part VI: Summary of the risk management plan

Summary of risk management plan for OPUVIZ (aflibercept)

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

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

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

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

I. The medicine and what it is used for

OPUVIZ is authorised in adults for 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), and visual impairment due to myopic choroidal neovascularisation (CNV). It contains aflibercept as the active substance and it is given by intravitreal injection.

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

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

Important risks of OPUVIZ, together with measures to minimise such risks and the proposed studies for learning more about OPUVIZ'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 PL 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 OPUVIZ, 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*.

II.A List of important risks and missing information

Important risks of OPUVIZ 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 OPUVIZ. 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 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-foetotoxicity
Missing information	None

II.B Summary of important risks

Important identified risk: Endophthalmitis (likely infectious origin)	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of aflibercept as reflected in the Product Information and the summary of safety concerns for the reference product EYLEA.
Risk factors and risk groups	Improper aseptic techniques used during the procedure represent a general risk factor for endophthalmitis. No specific groups at risk have been established for aflibercept.
Risk minimisation measures	Routine risk minimisation SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 2, 3, and 4

Important identified risk: Endophthalmitis (likely infectious origin)	
	Patients should be monitored a week following injection per the SmPC section 4.4. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay per the SmPC section 4.2 and 4.4. Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections <u>Additional risk minimisation</u> Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD

Important identified risk: Intraocular inflammation	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of aflibercept as reflected in the Product Information and the summary of safety concerns for the reference product EYLEA.
Risk factors and risk groups	Considering the unknown mechanism for this effect, general risk factors have not yet been established. As literature showed, some cases reported in aflibercept in the post-marketing phase were attributed to batches of syringes used for intravitreal injection included in specific lots of EYLEA kits (Greenberg, 2019).
Risk minimisation measures	<u>Routine risk minimisation</u> SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 2, 3, and 4 Patients should be monitored a week following injection per the SmPC section 4.4. Patients should be instructed to report any symptoms of intraocular inflammation per the SmPC section 4.4. Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections

Important identified risk: Intraocular inflammation	
	Additional risk minimisation Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD

Greenberg JP, Belin P, Butler J, Feiler D, Mueller C, Tye A, et al. Aflibercept-Related Sterile Intraocular Inflammation Outcomes. Ophthalmol Retina. 2019; 3(9): 753-9.

Important identified risk: Transient intraocular pressure increase	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of aflibercept as reflected in the Product Information and the summary of safety concerns for the reference product EYLEA.
Risk factors and risk groups	Specific risk factors and risk groups have not yet been established for aflibercept. Several studies suggest that eyes with a history of glaucoma are at a higher risk for IOP elevation following intravitreal injection with VEGF inhibitors (Levin, 2021). Special precaution is needed in patients with poorly controlled glaucoma and OPUVIZ should not be administered to patients, whose IOP is ≥30 mmHg. In addition to history of glaucoma, other potential risk factors proposed in the literature include the type of retinal pathology, volume of injected medication, and intraocular fluid dynamics (Levin, 2021). The risk factors identified for the chronic, sustained elevations in IOP include the total number of injections and a greater frequency of administration (Bracha, 2018).
Risk minimisation measures	Routine risk minimisation SmPC sections 4.2, 4.4, 4.8, and 4.9 PL sections 2 and 4 Patients should be monitored immediately following the injection per the SmPC section 4.2. Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimisation

Important identified risk: Transient intraocular pressure increase	
	Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD

Bracha P, Moore NA, Ciulla TA, WuDunn D, Cantor LB. The acute and chronic effects of intravitreal anti-vascular endothelial growth factor injections on intraocular pressure: A review. Survey of Ophthalmology. 2018; 63(3): 281-95.
Levin AM, Chaya CJ, Kahook MY, Wirostko BM. Intraocular Pressure Elevation Following Intravitreal Anti-VEGF Injections: Short- and Long-term Considerations. J Glaucoma. 2021; 30(12): 1019-26.

Important identified risk: Retinal pigment epithelium tear	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of aflibercept as reflected in the Product Information and the summary of safety concerns for the reference product EYLEA.
Risk factors and risk groups	Patients with wet AMD represent a known risk group for the spontaneous development of retinal pigment epithelial tears. Therefore, this population is at risk of retinal pigment epithelial tears development associated with VEGF inhibitors. The risk factors described in the literature for developing retinal pigment epithelial tears at baseline or during anti-VEGF therapy in patients with vascularised pigment epithelial detachment with wet AMD include (Sastre-Ibáñez, 2019): • retinal pigment epithelial detachment height above 400 μm • presence of microtears • presence of a subretinal cleft • fibrovascular retinal pigment epithelial detachment • history of photodynamic therapy. A high-risk patient for development of retinal pigment epithelium tears is defined as showing one or more of the risk factors at the beginning or during the course of an anti-VEGF treatment (Clemens, 2016). It has been hypothesised that there may be a greater risk of retinal pigment epithelial tear associated with aflibercept than with ranibizumab or bevacizumab, as aflibercept has a 140 stronger bond to VEGF than ranibizumab, but further

Important identified risk: Retinal pigment epithelium tear	
	studies are required to corroborate this hypothesis (Sastre-Ibáñez, 2019).
Risk minimisation measures	Routine risk minimisation SmPC sections 4.4 and 4.8 PL sections 2 and 4 Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimisation Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD

Clemens CR, Eter N. Retinal Pigment Epithelium Tears: Risk Factors, Mechanism and Therapeutic Monitoring. Ophthalmologica. 2016; 235(1): 1-9.
Sastre-Ibáñez M, Martínez-Rubio C, Molina-Pallete R, Martínez- López-Corell P, Wu L, Arévalo JF, et al. Retinal pigment epithelial tears. Journal Français d'Ophtalmologie. 2019; 42(1): 63-72.

Important identified risk: Cataract (especially of traumatic origin)	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of aflibercept as reflected in the Product Information and the summary of safety concerns for the reference product EYLEA.
Risk factors and risk groups	The risk factors and groups have not yet been established for aflibercept.
Risk minimisation measures	Routine risk minimisation SmPC sections 4.2, 4.4, and 4.8 PL sections 2, 3, and 4 Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimisation Educational materials: • Prescriber's guide and video

	• Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD

Important potential risk: Medication errors	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of aflibercept as reflected in the Product Information and the summary of safety concerns for the reference product EYLEA.
Risk factors and risk groups	The risk groups or risk factor for undesirable outcomes associated with medication errors have not yet been established for aflibercept.
Risk minimisation measures	<u>Routine risk minimisation</u> SmPC sections 4.2, 4.9, and 6.6 PL sections 1 and 3 Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections <u>Additional risk minimisation</u> Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD

Important potential risk: Off-label use and misuse	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of aflibercept as reflected in the Product Information and the summary of safety concerns for the reference product EYLEA.
Risk factors and risk groups	The specific risk factors or groups at risk have not yet been established for aflibercept.
Risk minimisation measures	<u>Routine risk minimisation</u> SmPC sections 4.1, 4.2, 4.3, 4.4, and 4.6 PL sections 1, 2, and 3 Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections

Important potential risk: Off-label use and misuse	
	<u>Additional risk minimisation</u> Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD

Important potential risk: Embryo-foetotoxicity	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of aflibercept as reflected in the Product Information and the summary of safety concerns for the reference product EYLEA.
Risk factors and risk groups	Women of childbearing potential represent a general risk group for these effects. Aflibercept should not be used during the whole pregnancy, however, the first trimester seems to be the most susceptible period of pregnancy to the adverse effects associated with aflibercept.

Important potential risk: Embryo-foetotoxicity	
Risk minimisation measures	Routine risk minimisation SmPC sections 4.4, 4.6, and 5.3 PL section 2 Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept as per the SmPC section 4.4 and 4.6. Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimisation Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD

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 OPUVIZ.

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

There are no studies required for OPUVIZ.

Part VII: Annexes

Annex 1 – EudraVigilance Interface 61
Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme 61
Annex 3 - Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan 63
Annex 4 - Specific adverse drug reaction follow-up forms 64
Annex 5 - Protocols for proposed and ongoing studies in RMP part IV 65
Annex 6 - Details of proposed additional risk minimisation activities (if applicable) 66
Annex 7 - Other supporting data (including referenced material) 68
Annex 8 – Summary of changes to the risk management plan over time 70

Annex 4 - Specific adverse drug reaction follow-up forms

Targeted follow-up questionnaire for endophthalmitis and intraocular inflammation

Questionnaire: Endophthalmitis and intraocular inflammation

To the Health Care Provider: Complete this form as a supplement to the Health Care Professional Adverse Event Follow-Up Form provided.

SECTION I- REFRENCE ID		
AER Number:	**STUDY ID:**	**PATIENT ID:**

SECTION II – REPORTER/PATIENT INFORMATION			
REPORTER: ☐ **Physician** ☐ **Nurse** ☐ **Other(Specify):**_____			
REPORTER CONTACT INFORMATION			
Name:			
Institution:			
Phone		**Fax:**	
Address			
Email:			
PATIENT INFORMATION			
Age [years]: *(at onset of event)*	**Gender:** ☐ **Male** ☐ **Female**	**Weight: unit:**	**Height: unit:**

SECTION III – PRODUCT INFORMATION (Opuviz)	
Therapy date *(dd/mm/yyyy):* ☐ **Ongoing**	
Indication:	**Number of Opuviz doses before the event:**____
Opuviz injected: ☐ **OS** ☐ **OD** ☐ **OU**	
If both eyes were injected, indicate if the same vial was used: ☐ **Yes** ☐ **No** **If no, please provide Batch number per eyes:** **OS**_____ **OD**_____	
Vial	

Questionnaire: Endophthalmitis and intraocular inflammation

Lot/Batch number:

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 ☐ UNK

Date and time of injection preparation:

What was used for injection?

☐ Injection needle Batch No:_____

☐ Syringe (Luer lock: ☐ Yes ☐ No)

☐ Glass ☐ Plastic, Batch No:_____

Where was the syringe for injection prepared?	If prepared in pharmacy, provide the name and contact details:
☐ Treatment/Examining room ☐ Off-site pharmacy ☐ On-site pharmacy	

How many hours did the prepared syringe stay at room temperature prior to administration?

_____

SECTION IV-ADVERSE EVENT INFORMATION

Event (as reported term) ☐ **OS** ☐ **OD** ☐ **OU**	**Start date** *(dd/mm/yyyy)*	**Or how much time after injection did the event occur** ***(approx.):***	**Stop date** *(dd/mm/yyyy):*	**Outcome** (recovered, not recovered, improved, recovered with sequelae, fatal, UNK):

Questionnaire: Endophthalmitis and intraocular inflammation

If stop date is UNK, provide the approximate event duration (days):				
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:**	☐ **UNK**
☐ **Culture taken on:** **From :** ☐ **OS** ☐ **OD** ☐ **OU** ☐ **Culture not taken/ UNK**	☐ **Positive for:** ☐ **OS** ☐ **OD** ☐ **OU**		☐ **Negative for:** ☐ **OS** ☐ **OD** ☐ **OU**	
Reporter causality comment:				
☐ **Related to Opuviz** ☐ **Related to intravitreal injection procedure** ☐ **Not related to Opuviz or intravitreal injection procedure**				
Alternative explanation (e.g. underlying disease/condition predisposing to the event):				

Action taken with product		
Specify below	**Date from** *(dd/mm/yyyy)*	**Date to** *(dd/mm/yyyy)*
☐ **Dose not changed**	**N/A**	**N/A**
☐ **Stopped**		**N/A**
☐ **Dose reduced** - New dose:		
☐ **Interrupted**		
☐ **UNK**	**N/A**	**N/A**
Did the event abate/stop after treatment stopped? ☐ **Yes** ☐ **No** ☐ **UNK**		
Did the event reoccur upon resuming treatment? ☐ **Yes** ☐ **No** ☐ **UNK**		

SECTION IV – RELEVANT CLINICAL SYMPTOMS *(to AE of Interest)* **Please indicate which eye was affected**		
Symptom	**Start Date**	**Stop Date**

Questionnaire: Endophthalmitis and intraocular inflammation

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

SECTION V- RELEVANT (intravitreal) CONCOMITANT / HISTORICAL MEDICATION						
Drug Name	**From** *(dd/mm/yyyy)*	**To** *(dd/mm/yyyy)*	**Ongoing?**	**Dose/ Number 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	**Start Date** *(dd/mm/yyyy)*	**Stop Date** *(dd/mm/yyyy)*	**Ongoing?**
☐ **Diabetes**			☐
☐ **Autoimmune disease, please specify:**			☐
☐ **Immunodeficiency, please specify:**			☐
☐ **Other, please specify:**			☐

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

Questionnaire: Endophthalmitis and intraocular inflammation

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

Please sign electronically: **If your signature is not yet configured on your computer, please follow the instruction when you click in the signature field**	**Signature:**

Annex 6 - Details of proposed additional risk minimisation activities

Draft key messages of the additional risk minimisation measures

The marketing authorisation holder (MAH) has agreed to provide EU educational material for OPUVIZ. Prior to launch and during the product's lifecycle in each Member State the 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 OPUVIZ is marketed, ophthalmological clinics where OPUVIZ 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 30G needle, and angle of injection
- The vial is for single use only
- The need to expel excess volume of the syringe before injecting OPUVIZ 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 OPUVIZ

The patient information pack of the educational material includes a patient information guide and its audio version. The patient information guide contains following key elements:

- Patient information leaflet
- Who should be treated with OPUVIZ
- How to prepare for OPUVIZ treatment
- What are the steps following treatment with OPUVIZ
- 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 OPUVIZ