SANDOZ

Patient Safety & Pharmacovigilance

SOK583 (INN: aflibercept)
40 mg/mL
Solution for injection

SOK583/aflibercept

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Aflibercept
Product(s) concerned (brand name(s)):	Afqlir
Document status:	Final
Version number:	1.2
Data lock point for this RMP	14-Jul-2023
Date of final sign off	16-Jul-2024
Number of pages	65

Rationale for submitting an updated RMP:

As done for other approved biosimilars for aflibercept, an injection procedure video was included in the educational material as requested by PRAC review comments in the Day 180 List of Outstanding Issues.

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v1.1
Part I	None
Part II	None
Part III	None
Part IV	None
Part V	Updates in alignment with changes made in Part VII, Annex 6
Part VI	None
Part VII	Annex 4: Alignment of the questionnaire on endophthalmitis and intraocular inflammation with that of the updated Eylea RMP Annex 6: Inclusion of an injection procedure video as done for other biosimilars of aflibercept as requested by PRAC review comments in the Day 180 List of Outstanding Issues

Other RMP versions under evaluation

No RMP versions are currently under evaluation.

QPPV name: Dr Juergen Maares

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

Table of contents

List of tables

List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse event
CI	Confidence interval
CNV	Choroidal neovascularisation
DME	Diabetic macular oedema
eCRS	Electronic Case Retrieval Strategy
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
Eylea EU	EU-authorized Eylea®; the registered trademark sign "®" will be omitted from all following instances of Eylea EU in the document
MedDRA	Medical Dictionary for Regulatory Activities
nAMD	Neovascular (wet) age-related macular degeneration
PlGF	Placental growth factor
PFS	Prefilled syringe
PL	Patient leaflet
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
ROP	Retinopathy of prematurity
RPE	Retinal pigment epithelial
RVO	Retinal vein occlusion (CRVO: central RVO; BRVO: branch RVO)
SAE	Serious adverse event
SAF	Safety analysis set
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	System organ class
SOK583	Sandoz' aflibercept biosimilar product to Eylea; this code was used during development of Afqlir
TEAE	Treatment-emergent adverse event
VEGF	Vascular endothelial growth factor

1 Part I: Product(s) Overview

Table 1-1 Part I.1 - Product Overview

Active substance(s) (INN or common name)	Aflibercept
Pharmacotherapeutic group(s) (ATC Code)	Ophthalmologicals / antineovascularisation agents (S01LA05)
Marketing Authorization Applicant	Sandoz GmbH, Kundl, Austria
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Afqlir (proposed)
Marketing authorization procedure	centralized
Brief description of the product	Chemical class: Aflibercept is a fusion protein consisting of portions of human VEGF (Vascular Endothelial Growth Factor) receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors.
	Summary of mode of action: 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 synergize with VEGF-A in these processes and is also known to promote leucocyte infiltration and vascular inflammation.
	Important information about its composition: Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.
Hyperlink to the Product Information	[1.3.1 Proposed SmPC]
Indication(s) in the EEA	Current: • 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)
	Proposed: Currently not applicable
Dosage in the EEA	Current (if applicable): The injection volume of Afqlir is 0.05 mL (equivalent to 2 mg aflibercept)

	Wet AMD The recommended dose for Afqlir is 2 mg aflibercept, equivalent to 0.05 ml. Macular edema secondary to RVO (branch RVO or central RVO) The recommended dose for Afqlir is 2 mg aflibercept, equivalent to 0.05 ml. Diabetic macular oedema The recommended dose for Afqlir is 2 mg aflibercept, equivalent to 0.05 ml. Myopic CNV The recommended dose for Afqlir is 2 mg aflibercept, equivalent to 0.05 ml.
	Proposed: Currently not applicable
Pharmaceutical form(s) and strengths	Current: Solution for injection (injection) The solution is a clear, colourless to slightly brownish yellow and iso-osmotic solution. • Solution for injection in a pre-filled syringe. Each pre-filled syringe contains 6.6 mg aflibercept in 0.165 ml (40 mg/ml) in iso-osmotic solution. This provides a usable amount to deliver a single dose of 0.05 ml containing 2 mg aflibercept. • Solution for injection in a vial. Each vial contains 9.6 mg aflibercept in 0.240 ml (40 mg/ml) in iso-osmotic solution. This provides a usable amount to deliver a single dose of 0.05 ml containing 2 mg aflibercept.
	Proposed: Currently not applicable
Is/will the product be patient to additional monitoring in the EU?	Yes

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

As agreed with Health Authorities and in line with EMA, FDA, and WHO guidance on the use of animal studies for the evaluation of biosimilars, comparative non-clinical in vivo studies were not required with SOK583 to support approval .

A panel of in vitro physicochemical and in vitro functional studies were conducted to compare SOK583 and Eylea. No clinically meaningful differences in the structure, composition, and biological activity were identified between the SOK583 and EU-authorized and US-licensed Elyea.

Non-clinical studies performed by Regeneron demonstrated that the toxicity of aflibercept is related to its pharmacology (FDA Eylea 2011). Thus, the in vitro functional assays were considered predictive for any potential toxicological effects of SOK583. As these in vitro assays are more sensitive than in vivo studies, and as SOK583 and Eylea showed similar potency in vitro, no differences in toxicity were expected between the products in animal studies and such studies were thereby not deemed necessary.

All SOK583 presentations share the same alternative formulation in comparison to Eylea; this alternative formulation employs widely used excipients that have already been approved for other drugs indicated for intravitreal use (e.g. Lucentis® (ranibizumab)). Differences between SOK583 and Eylea in formulations were not considered to constitute any safety issue and did not justify the performance of any ocular toxicity study in animals.

Given the similarity between SOK583 and Eylea demonstrated in in vitro physicochemical and in vitro functional studies, the findings from non-clinical in vivo studies with the reference product Eylea are considered relevant for SOK583 (FDA Eylea 2011, EMA Eylea 2013).

3 Part II: Module SIII - Clinical trial exposure

The SOK583 clinical development program consisted of 1 pivotal efficacy, safety, and immunogenicity study CSOK583A12301 and 2 supportive safety studies CSOK583A12303 and CSOK583A12304.

Study CSOK583A12301 was a 52-week multicenter, randomized, double-masked, 2-arm parallel study to demonstrate similar efficacy and to show comparable safety and immunogenicity between SOK583 and Eylea EU in patients with nAMD, 50 years or older and naïve to anti-VEGF treatment. Patients were randomized 1:1 and received up to 8 intravitreal injections of SOK583 or Eylea-EU in the study eye at doses of 2 mg/0.05 mL. The treatment schedule was in line with the Eylea SmPC (2024).

The study met its objectives and demonstrated similar efficacy and showed comparable safety and immunogenicity between SOK583 and Eylea EU. In addition, systemic aflibercept concentrations were comparable between the 2 treatment groups.

Note that Study CSOK583A12301 was ongoing when this RMP was prepared, and safety data are provided with the data cutoff date 15-Feb-2023. This includes all safety data available at the time when the last patient completed Week 40. At the data cutoff date, 443 of the 484 patients treated in the study had completed Week 40 and 259 patients had completed the study. Interim database lock was on 14-Apr-2023.

Patient exposure in Study CSOK583A12301 is summarized in Table 3-1 to Table 3-3.

Studies CSOK583A12303 and CSOK583A12304 were open-label, single-arm, multicenter studies in patients with nAMD to evaluate the safety of SOK583 provided in a vial kit (CSOK583A12303) or a prefilled syringe (CSOK583A12304). Study patients were 50 years or older and had previously received intravitreal treatment with Eylea. Patients received a single injection of SOK583 in the study eye at a dose of 2 mg/0.05 mL. Both studies were requested by FDA to support the human factors evaluation of the SOK583 drug-device combination products and were conducted exclusively in the US.

In both studies, the observed safety profile of SOK583 was in line with the established safety profile of Eylea.

In studies CSOK583A12303 and CSOK583A12304, a total of 66 patients received a single intravitreal injection of 2 mg/0.05 mL SOK583, amounting to a patient exposure of 0.18 years. Both studies combined included 39 female and 27 male patients. Patients' age ranged from 62 to 102 years, and all patients were white.

The nature and patterns of TEAEs observed in the 3 studies were in line with the Eylea SmPC (2024). No new or unexpected safety issues arose during the studies.

Table 3-1 Duration of exposure in Study CSOK583A12301 (SAF)

Duration (days)	SOK583 N=244	Patient exposure (years)	Eylea EU N=240	Patient exposure (years)
n (%)	244 (100.0)	212.3	240 (100.0)	208.9
Mean (SD)	317.7 (60.80)		317.9 (63.29)	
Median	337.0		337.0	
Min, Max	1, 351		1, 352	

Duration of exposure (days) is defined as (Date of last treatment dose date - first dose date+1)
Patient exposure (years) : (sum of duration of exposure for all patients who were administered study drug (days)) / 365.25

Table 3-2 Duration of exposure by sex and age group in Study CSOK583A12301 (SAF)

Sex Age (years)	Duration (days)	SOK583 N=244	Patient exposure (years)	Eylea EU N=240	Patient exposure (years)
Female					
Overall	n (%)	138 (56.6)	117.9	136 (56.7)	115.8
	Mean (SD)	312.1 (72.38)		310.9 (73.39)	
	Median	337.0		337.0	
	Min, Max	1, 351		1, 352	
< 75	n (%)	53 (21.7)	45.5	51 (21.3)	43.1
	Mean (SD)	313.4 (65.17)		308.7 (84.27)	
	Median	337.0		337.0	
	Min, Max	56, 349		1, 352	
≥ 75	n (%)	85 (34.8)	72.5	85 (35.4)	72.7
	Mean (SD)	311.4 (76.89)		312.2 (66.51)	
	Median	337.0		336.0	
	Min, Max	1, 351		1, 350	
Male					
Overall	n (%)	106 (43.4)	94.3	104 (43.3)	93.1
	Mean (SD)	325.0 (40.31)		327.1 (45.66)	
	Median	337.0		337.0	
	Min, Max	112, 350		1, 350	
< 75	n (%)	50 (20.5)	45.1	47 (19.6)	42.3
	Mean (SD)	329.6 (39.52)		329.0 (37.26)	
	Median	337.0		337.0	
	Min, Max	112, 350		106, 350	
≥ 75	n (%)	56 (23.0)	49.2	57 (23.8)	50.8
	Mean (SD)	321.0 (40.92)		325.6 (51.86)	
	Median	337.0		337.0	
	Min, Max	167, 346		1, 350	

Duration of exposure (days) is defined as (Date of last treatment dose date - first dose date+1)
Patient exposure (years) : (sum of duration of exposure for all patients who were administered study drug (days)) / 365.25

Table 3-3 Duration of exposure by race in Study CSOK583A12301 (SAF)

Race	Duration (days)	SOK583 N=244	Patient exposure (years)	Eylea EU N=240	Patient exposure (years)
Overall	n (%)	244 (100.0)	212.3	240 (100.0)	208.9
	Mean (SD)	317.7 (60.80)		317.9 (63.29)	
	Median	337.0		337.0	
	Min, Max	1, 351		1, 352	
White	n (%)	216 (88.5)	188.1	214 (89.2)	187.3
	Mean (SD)	318.1 (61.24)		319.7 (57.58)	
	Median	337.0		337.0	
	Min, Max	1, 351		1, 352	
Black or African American	n (%)	0 (0.0)		1 (0.4)	0.9
	Mean (SD)			338.0	
	Median			338.0	
	Min, Max			338, 338	
Asian	n (%)	16 (6.6)	14.2	12 (5.0)	9.3
	Mean (SD)	323.6 (38.62)		282.2 (131.39)	
	Median	337.0		337.0	
	Min, Max	225, 344		1, 344	
Missing	n (%)	12 (4.9)	10.0	13 (5.4)	11.4
	Mean (SD)	303.6 (77.80)		319.8 (61.18)	
	Median	336.0		335.0	
	Min, Max	112, 343		117, 344	

Duration of exposure (days) is defined as (Date of last treatment dose date - first dose date+1)
Patient exposure (years) : (sum of duration of exposure for all patients who were administered study drug (days)) / 365.25

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

This MAA has been submitted for a similar biological medicinal product under Article 10 (4) of Directive 2001/83/EC, as amended; therefore, a tailored clinical program was justified.

In the clinical development of SOK583 as a similar biological medicinal product to Eylea, a confirmatory efficacy, safety, and immunogenicity study (CSOK583A12301) was conducted in patients with nAMD who were 50 years or older and naïve to anti-VEGF treatment based on scientific discussions with EMA. In addition, 2 supportive single-arm safety studies (CSOK583A12303 and CSOK583A12304) were conducted in patients with nAMD who were 50 years or older and had previously received intravitreal treatment with Eylea. Both studies were requested by FDA to support the human factors evaluation of the SOK583 combination product and were conducted exclusively in the US.

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

The exclusion criteria applied in the clinical studies with SOK583 aimed at optimizing the study conduct and minimizing bias and confounding of study results. Therefore, all exclusion criteria were related to technical reasons and not to safety concerns. In line with the current Eylea RMP, none of the exclusion criteria were considered missing information.

For a biosimilar clinical development, the objective is not to establish the safety profile de novo or expand it by generating data for missing information. Instead, the aim is to confirm that the biosimilar's safety profile is in line with the one established for the reference product. The study design and exclusion criteria were chosen accordingly.

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

Clinical trial experience with SOK583 comprises 310 patients with nAMD treated for up to 52 weeks.

The SOK583 clinical development program 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.

Based on the totality of data, including analytical, functional, and clinical PK, efficacy, safety, and immunogenicity data, biosimilarity between SOK583 and Eylea has been shown. Therefore, the same positive benefit-risk ratio and the safety profile established for Eylea apply to SOK583.

4.3 SIV.3 Limitations in respect to populations typically underrepresented in clinical trial development programs

Children

Only patients 50 years or older were included in the 3 studies with SOK583. Clinical trial experience with SOK583 in children is therefore not available.

In line with the Pediatric Regulation (EC) No. 1901/2006, of the European Parliament and of the Council of 12-Dec-2006 on medicinal products for pediatric use, SOK583, as a similar

biological medicinal product, has been exempted from the requirement to submit a Pediatric Investigational Plan (PIP).

Eylea is indicated in preterm infants for the treatment of retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease. However, the safety and efficacy of Eylea in children and adolescents below 18 years of age for indications other than ROP have not been established, and there is no relevant use of Eylea in the pediatric population for the indications of wet AMD, CRVO, BRVO, DME and myopic CNV (Eylea SmPC 2024).

Sandoz is not seeking approval of SOK583 in ROP in preterm infants. The missing information listed for Eylea "Long-term safety of aflibercept in preterm infants with ROP" is therefore not applicable.

Elderly

Most (288/310) patients treated in the 3 studies with SOK583 were 65 years or older. Clinical trial experience with SOK583 in the elderly population is therefore available.

Pregnant or breastfeeding women

Pregnant or breastfeeding women were excluded from clinical trials with SOK583. Clinical trial experience with SOK583 in pregnant or breastfeeding women is therefore not available.

Hepatic and/or renal impairment

In line with the Eylea SmPC (2024), patients with hepatic and/or renal impairment were not specifically studied with SOK583.

Table 4-1 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Patients included in the 3 studies could have medical histories of the relevant comorbidities listed.
Population with relevant different ethnic origin	Not included in the clinical development program
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other	
• Children	Not included in the clinical development program
• Elderly	Overall, 288/310 patients treated with SOK583 were 65 years or older. Study CSOK583A12301: 225/244 patients treated with SOK583 were ≥ 65 years; mean age

Type of special population	Exposure
	of patients treated with SOK583 was 75.8 years (range: 53 to 94 years). Study CSOK583A12303: 33/36 patients treated with SOK583 were ≥ 65 years; mean age of patients treated with SOK583 was 80.9 years (range: 62 to 102 years). Study CSOK583A12304: 30/30 patients treated with SOK583 were ≥ 65 years; mean age of patients treated with SOK583 was 79.4 years (range: 66 to 92 years).

5 Part II: Module SV - Post-authorization experience

SOK583 is not yet marketed in any country. This section is therefore not applicable.

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

6.1 Potential for misuse for illegal purposes

No potential for misuse or illegal purposes is currently anticipated for aflibercept.

7 Part II: Module SVII - Identified and potential risks

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

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

Not all adverse reactions are necessarily considered an important risk for the medicinal product in a given therapeutic context, and not all risks qualify as sufficiently important to be included in the list of safety concerns for the purpose of risk management planning.

No new safety signal has been observed in the SOK583 development program. Therefore, there were no risks considered necessary for inclusion in the list of safety concerns.

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

Based on the totality of data, including analytical, functional, and clinical PK, efficacy, safety, and immunogenicity data, biosimilarity between SOK583 and Eylea has been shown. Therefore, the safety concerns of SOK583 are the same as those for the reference product Eylea (Bayer EMA 2024).

Table 7-1 Important identified risks

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
Endophthalmitis (likely infectious origin)	Endophthalmitis is an intraocular infection that may be caused by the intravitreal injection procedure if there is a break in sterile technique. Source of infectious agents is in most cases the patient's conjunctival bacterial flora. Endophthalmitis carries the risk of severe vision loss. This risk was identified in the pivotal studies of the Eylea clinical development program. Endophthalmitis and related cases were not observed in the SOK583 clinical development program. Endophthalmitis (likely infectious origin) is an important identified risk of the reference product Eylea and therefore applicable to SOK583.
Intraocular inflammation	Intraocular inflammation may occur without an infectious origin and may lead to generalized eye inflammation and risk of blindness. This risk was identified in the pivotal studies of the Eylea clinical development program. Intraocular inflammation and related cases were also observed in the SOK583 clinical development program.

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
	Intraocular inflammation is an important identified risk of the reference product Eylea and therefore applicable to SOK583.
Transient intraocular pressure increase	Intravitreal injection of the drug will lead to an increase in the volume of the vitreous body, which results in a transient increase of intraocular pressure. This risk was identified in the pivotal studies of the Eylea clinical development program. Transient intraocular pressure increased was also observed in the SOK583 clinical development program. Transient intraocular pressure increased is an important identified risk of the reference product Eylea and therefore applicable to SOK583.
Retinal pigment epithelial tears	Retinal pigment epithelial tears are attributed to a decrease in intracellular adherence, which increases the susceptibility to tearing of the RPE layer. This risk was identified in the pivotal studies of the Eylea clinical development program. Cases of retinal epithelial tears were also observed in the SOK583 clinical development program. Retinal pigment epithelial tears is an important identified risk of the reference product Eylea and therefore applicable to SOK583.
Cataract (especially of traumatic origin)	During intravitreal injection, a traumatic cataract may be caused when the needle touches the lens. This risk was identified in the pivotal studies of the Eylea clinical development program. Cataract (especially of traumatic origin) cases were not observed in the SOK583 clinical development program. Cataract (especially of traumatic origin) is an important identified risk of the reference product Eylea and therefore applicable to SOK583.

Table 7-2 Important potential risks

Risk	Risk-benefit impact (Reasons for classification as important potential risk)
Medication errors	Due to an excess volume in the SOK583 vial and PFS, which exceeds the recommended dose of 2 mg aflibercept per injection, injecting more than the approved volume would result in overdose. However, this numerical overdose is limited, and the drug will be administered only by qualified physicians (not by patients). This

Risk	Risk-benefit impact (Reasons for classification as important potential risk)
	reduces the risk of inappropriate dosing and administration as well. With Eylea, no clinically meaningful events of overdose have been reported so far (neither in clinical studies nor in usual care). Nevertheless, it was decided to consider “medication error” a potential risk of treatment, which is, however, completely avoidable by proper adherence to the dosing recommendations. No events of overdose or medication errors have been reported in clinical studies with SOK583. Medication errors is an important potential risk of the reference product Eylea and therefore applicable to SOK583.
Off-label use and misuse	As with other drugs, aflibercept might be intentionally used other than recommended, or in clinical conditions outside the approved indications. Aflibercept does not have any dependence potential. Since the clinical experience with aflibercept in such off-label use is limited (in particular in terms of efficacy and safety), any case of off-label use is currently considered an important potential risk. In addition, intentional off-label use in the context of multiple use of single use product (vial splitting) has been observed with Eylea. Off-label use and misuse is an important potential risk of the reference product Eylea and therefore applicable to SOK583.
Embryo-fetotoxicity	As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following systemic administration of anti-VEGF therapies might result in adverse effects on pregnancy. The current experience with intravitreal-administered anti-VEGF therapies in pregnancy is sparse (single cases reported only) and thus inconclusive. However, early loss of pregnancy after intravitreal bevacizumab injection has been reported in a very few instances. Therefore, particular attention is paid to that safety issue. No cases of embryo-fetotoxicity were reported during the clinical development program; however, pregnant females were excluded from clinical study participation. Current postmarketing surveillance data of Eylea do not suggest an increased risk of embryo-fetotoxicity on treatment with aflibercept. Embryo-fetotoxicity is an important potential risk of the reference product Eylea and therefore applicable to SOK583.

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

This is the initial RMP for SOK583. This section is therefore not applicable.

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

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

7.3.1.1 Important Identified Risk: Endophthalmitis (likely infectious origin)

Table 7-3 Important identified risk: Endophthalmitis (likely infectious origin): Other details

Endophthalmitis (likely infectious origin)	Details
MedDRA search terms (MedDRA 26.0)	Bacterial endophthalmitis; Candida endophthalmitis; Endophthalmitis; Mycotic endophthalmitis; Non-infectious endophthalmitis; Panophthalmitis; Pseudoendophthalmitis
Potential mechanisms	Endophthalmitis is an intraocular infection that may be caused by the intravitreal injection procedure if there is a break in sterile technique. Source of infectious agents is in most cases the patient's conjunctival bacterial flora.
Evidence source(s) and strength of evidence	This risk was identified in the pivotal studies of the Eylea clinical development program.
Characterization of the risk:	**Frequency:** Endophthalmitis was not observed in the SOK583 clinical development program. As per the Eylea SmPC (2024), serious ocular adverse reactions in the study eye related to the injection procedure have occurred in less than 1 in 1,900 intravitreal injections with Eylea and included blindness, endophthalmitis, retinal detachment, cataract traumatic, cataract, vitreous haemorrhage, vitreous detachment, and intraocular pressure increased. Culture positive and culture negative endophthalmitis is listed as uncommon (≥ 1/1000 to < 1/100) treatment-emergent ADR. **Severity:** Severe events of endophthalmitis were reported for Eylea in the Eylea pivotal studies. **Reversibility and long-term outcome:** Patients should report to their doctors any signs or symptoms of intraocular inflammation (e.g. visual acuity decreased, pain, photophobia, or redness) in order to enable the treating physician to introduce appropriate countermeasures in due time. Treatment should be initialized as soon as possible and depends on cause and severity. Treatment may consist of topical and intravitreal application of antibiotics, corticosteroids, and surgical removal of matter and infected structures (drainage, vitrectomy). **Impact on quality of life:** Endophthalmitis can cause permanent loss of vision if it is not diagnosed at an early stage and appropriately treated. Vision loss as such constitutes a substantial burden for the involved subject.

Endophthalmitis (likely infectious origin)	Details
Risk factors and risk groups	Risk factors include improper aseptic injection technique, which increases the risk of intraocular infection such as endophthalmitis.
Preventability	The risk of intraocular infection/inflammation such as endophthalmitis, especially if caused by pathogens, cannot be completely excluded, but can be minimized by working under strict aseptic and sterile conditions. Therefore, only experienced and appropriately trained ophthalmologists should be charged with the injection procedure.
Impact on the benefit-risk balance of the product	Educational material is provided as an additional risk minimization measure to raise patients' and physicians' awareness on identified and potential risks. Furthermore, a specific follow-up checklist is used for received adverse event reports about this risk in order to gain more knowledge about this risk. This important identified risk was considered in the product benefit-risk assessment, which is positive.
Public health impact	Severe intraocular infection such as endophthalmitis can cause permanent loss of vision if it is not rapidly diagnosed and appropriately treated. This condition is likely to impact the ability to work and to increase the dependency on caregivers.

7.3.1.2 Important Identified Risk: Intraocular inflammation

Table 7-4 Clinical trial data of intraocular inflammation (Study CSOK583A12301)

	SOK583 N=244 n (%) 95% CI	Eylea EU N=240 n (%) 95% CI
Number of subjects with at least 1 event	0 (0.0) (0.00, 1.50)	2 (0.8) (0.10, 2.98)
Maximum severity / grade		
Mild	0 (0.0)	1 (0.4)
Moderate	0 (0.0)	1 (0.4)
Severe	0 (0.0)	0 (0.0)
SAEs	0 (0.0)	0 (0.0)
AE Outcome		
Recovered/Resolved	0 (0.0)	2 (0.8)
Recovering/Resolving	0 (0.0)	0 (0.0)
Not Recovered/Not Resolved	0 (0.0)	0 (0.0)
Recovered/Resolved with sequelae	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)
Leading to Death	0 (0.0)	0 (0.0)

MedDRA version 26.0, Case Retrieval Strategy version 29-Apr-2023
Maximum Severity is counted as per risk name as defined with eCRS.
Confidence Interval is calculated using Exact Confidence Interval for Binomial Proportions.

Table 7-5 Important identified risk: Intraocular inflammation: Other details

Intraocular inflammation	Details
MedDRA search terms (MedDRA 26.0)	Anterior chamber inflammation; Chorioretinitis; Choroiditis; Cyclitis; Eye infection intraocular; Eye inflammation; Hypopyon; Infective uveitis; Iridocyclitis; Iritis; Necrotising retinitis; Non-infectious endophthalmitis; Noninfective chorioretinitis; Noninfective retinitis; Ocular vasculitis; Retinal vasculitis; Retinitis; Uveitis; Viral keratouveitis; Viral uveitis; Vitreous abscess; Vitritis; Vitritis infective
Potential mechanisms	Intraocular inflammation may occur without an infectious origin, i.e. where no pathogens can be identified (either no culture performed or negative culture growth). This condition is also referred to as “sterile” inflammation. The cause of a sterile inflammation, independently of the administered drug, remains uncertain, and a multifactorial origin (including intravitreal anti-VEGF therapies, silicon oil from syringes, or immune reactions; Anderson et al 2021) cannot be excluded.
Evidence source(s) and strength of evidence	This risk was identified in the pivotal studies of the Eylea clinical development program.
Characterization of the risk:	**Frequency:** In Study CSOK583A12301, intraocular inflammation was reported for 2/240 patients in the Eylea EU group (Table 7-4). In the supportive studies CSOK583A12303 and CSOK583A12304, intraocular inflammation was not observed. As per the Eylea SmPC (2024), serious ocular adverse reactions in the study eye related to the injection procedure have occurred in less than 1 in 1,900 intravitreal injections with Eylea and included blindness, endophthalmitis, retinal detachment, cataract traumatic, cataract, vitreous haemorrhage, vitreous detachment, and intraocular pressure increased. Culture positive and culture negative endophthalmitis is listed as uncommon (≥ 1/1000 to < 1/100) treatment-emergent ADR. **Severity:** Most events of intraocular inflammation reported for Eylea in the Eylea pivotal studies were of mild severity; moderate or severe events were also reported, but at low frequencies. The events of intraocular inflammation observed in Study CSOK583A12301 were non-serious and of mild and moderate severity. **Reversibility and long-term outcome:** Patients should report to their doctors any signs or symptoms of intraocular inflammation (e.g. visual acuity decreased, pain, photophobia, or redness) in order to enable the treating physician to introduce appropriate countermeasures in due time. Treatment should be initialized as soon as possible and depends on cause and severity. Treatment may consist of topical and intravitreal application of antibiotics, corticosteroids, and surgical removal of matter and infected structures (drainage, vitrectomy). **Impact on quality of life:** An intraocular inflammation generally constitutes a serious condition, which may lead to generalized eye inflammation and risk of blindness. Vision loss as such constitutes a substantial burden for the involved subject.
Risk factors and risk groups	Intraocular inflammation is a known risk of intravitreal injections of anti-VEGFs and other intravitreal applied drugs. Among the factors discussed to contribute to this risk are intravitreal anti-VEGF therapies, silicon oil from syringes, or immune reactions.

Intraocular inflammation	Details
Preventability	Measures other than aseptic injection techniques to prevent infectious reactions are not known to minimize the risk of intraocular inflammation. It is crucial to work under strict aseptic and sterile conditions. Therefore, only experienced and appropriately trained ophthalmologists should be charged with the injections.
Impact on the benefit-risk balance of the product	Educational material is provided as an additional risk minimization measure to raise patients' and physicians' awareness on identified and potential risks. Furthermore, a specific follow-up checklist is used for received adverse event reports about this risk in order to gain more knowledge about this risk. This important identified risk was considered in the product benefit-risk assessment, which is positive.
Public health impact	Severe intraocular infection/inflammation can cause permanent loss of vision, if it is not rapidly diagnosed and appropriately treated. This condition is likely to impact the ability to work and to increase the dependency on caregivers.

7.3.1.3 Important Identified Risk: Transient intraocular pressure increase

Table 7-6 Clinical trial data of transient intraocular pressure increase (Study CSOK583A12301)

	SOK583 N=244 n (%) 95% CI	Eylea EU N=240 n (%) 95% CI
Number of subjects with at least 1 event	3 (1.2) (0.25, 3.55)	8 (3.3) (1.45, 6.46)
Maximum severity / grade		
Mild	3 (1.2)	6 (2.5)
Moderate	0 (0.0)	2 (0.8)
Severe	0 (0.0)	0 (0.0)
SAEs	0 (0.0)	0 (0.0)
AE Outcome		
Recovered/Resolved	3 (1.2)	8 (3.3)
Recovering/Resolving	0 (0.0)	1 (0.4)
Not Recovered/Not Resolved	0 (0.0)	0 (0.0)
Recovered/Resolved with sequelae	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)
Leading to Death	0 (0.0)	0 (0.0)

MedDRA version 26.0, Case Retrieval Strategy version 29Apr2023
Maximum Severity is counted as per risk name as defined with eCRS.
Confidence Interval is calculated using Exact Confidence Interval for Binomial Proportions.

Table 7-7 Important identified risk: Transient intraocular pressure increase: Other details

Transient intraocular pressure increase	Details
MedDRA search terms (MedDRA 26.0)	Episcleral venous pressure increased; Intraocular pressure fluctuation; Intraocular pressure increased; Intraocular pressure test abnormal; Ocular hypertension
Potential mechanisms	Intravitreal injection of the drug, which is dissolved in a certain amount of injection liquid, will lead to an increase in the volume of the vitreous body (volume effect). This volume increase results in a transient intraocular pressure increase until the surplus fluid has been resorbed from the inner eye.
Evidence source(s) and strength of evidence	This risk was identified in the pivotal studies of the Eylea clinical development program.
Characterization of the risk:	**Frequency:** In Study CSOK583A12301, transient intraocular pressure was reported for comparable numbers and proportions of patients in the SOK583 and Eylea EU groups (Table 7-6). In the supportive studies CSOK583A12303 and CSOK583A12304, intraocular pressure was to be measured within 5 minutes after injection, and values ≥ 26 mmHg and increases in intraocular pressure ≥ 10 mmHg were to be reported as TEAEs. Transient TEAEs of intraocular pressure increased were reported for 15/36 patients (41.7%) in Study CSOK583A12303, 6 of which were related to study procedure; one of these events was related to both study treatment and study procedure and one was related to study treatment. In Study CSOK583A12304, a transient TEAE of intraocular pressure increased was reported for 1/30 patient (3.3%) that was not related to study treatment or study procedure. In all 3 studies, TEAEs of intraocular pressure increased resolved within 60 minutes. As per the Eylea SmPC (2024), serious ocular adverse reactions in the study eye related to the injection procedure have occurred in less than 1 in 1,900 intravitreal injections with Eylea. Intraocular pressure increased (8%) was among the most frequently observed adverse reactions to Eylea and is listed as a common (≥ 1/100 to < 1/10) treatment-emergent ADR. **Severity:** Most events of intraocular pressure increased observed for Eylea in the Eylea pivotal studies were of mild severity; moderate or severe events were also reported, but at low frequencies. In Study CSOK583A12301, all events of transient intraocular pressure increased were mild. In Studies CSOK583A12303 and CSOK583A12304, most TEAEs of intraocular pressure increased were mild; 1 TEAE was moderate and not related to study treatment or study procedure. **Reversibility and long-term outcome:** There is the risk that elevated eye pressure results in glaucoma, which is characterized by a loss of nerve fibers in the optic nerve with the subsequent risk of blindness. However, increased intraocular pressure is not a mandatory prerequisite for the development of glaucoma. Transient intraocular pressure increase is usually a mild reaction. Intraocular pressure generally normalizes back to baseline values within 0.5 to 1 hours after injection. Patients recovered without sequelae. **Impact on quality of life:** Increases in the intraocular pressure after intravitreal injection are usually transient, and there is no robust evidence

Transient intraocular pressure increase	Details
	so far that even after multiple injections could become durable or may lead to clinically relevant glaucoma.
Risk factors and risk groups	Patients with glaucoma. Transient intraocular pressure increase following intravitreal injection is a well-known side effect of any intravitreal administration of liquids used for drug dissolution.
Preventability	Intraocular pressure should be checked after each injection. The transient increase of eye pressure is an inherent result of the procedure-related volume load of intravitreal injections; therefore, it cannot be prevented.
Impact on the benefit-risk balance of the product	Educational material is provided as an additional risk minimization measure to raise patients' and physicians' awareness on identified and potential risks. This important identified risk was considered in the product benefit-risk assessment, which is positive.
Public health impact	Transient intraocular pressure increase is usually transient and mild. Therefore, no public health impact is expected from this safety concern.

7.3.1.4 Important Identified Risk: Retinal pigment epithelial tears

Table 7-8 Clinical trial data of retinal pigment epithelial tear (Study CSOK583A12301)

	SOK583 N=244 n (%) 95% CI	Eylea EU N=240 n (%) 95% CI
Number of subjects with at least 1 event	10 (4.1) (1.98, 7.41)	7 (2.9) (1.18, 5.92)
Maximum severity / grade		
Mild	3 (1.2)	0 (0.0)
Moderate	7 (2.9)	7 (2.9)
Severe	0 (0.0)	0 (0.0)
SAEs	0 (0.0)	0 (0.0)
AE Outcome		
Recovered/Resolved	1 (0.4)	0 (0.0)
Recovering/Resolving	2 (0.8)	1 (0.4)
Not Recovered/Not Resolved	7 (2.9)	6 (2.5)
Recovered/Resolved with sequelae	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)
Leading to Death	0 (0.0)	0 (0.0)

MedDRA version 26.0, Case Retrieval Strategy version 29Apr2023
Maximum Severity is counted as per risk name as defined with eCRS.
Confidence Interval is calculated using Exact Confidence Interval for Binomial Proportions.

Table 7-9 Important identified risk: Retinal pigment epithelial tears: Other details

Retinal pigment epithelial tears	Details
MedDRA search terms (MedDRA 26.0)	Retinal pigment epithelial tears
Potential mechanisms	Retinal pigment epithelial tears are attributed to a decrease in intracellular adherence, which increases the susceptibility to tearing of the RPE layer. Tears in the RPE layer may occur secondary to AMD, following intravitreal injections, or for unknown reasons.
Evidence source(s) and strength of evidence	This risk was identified in the pivotal studies of the Eylea clinical development program.
Characterization of the risk:	**Frequency:** In Study CSOK583A12301, retinal pigment epithelial tears were reported for comparable numbers and proportions of patients in the SOK583 and Eylea EU groups (Table 7-8). In the supportive studies CSOK583A12303 and CSOK583A12304, retinal pigment epithelial tears were not observed in patients treated with SOK583. As per the Eylea SmPC (2024), retinal pigment epithelial tears were observed in wet AMD studies only and are listed as common (≥ 1/100 to < 1/10) treatment-emergent ADR. **Severity:** Most events of retinal pigment epithelial tears observed for Eylea in the Eylea pivotal studies were of mild or moderate severity; severe events were also reported, but at low frequencies. In Study CSOK583A12301, most events of retinal pigment epithelial tears were of moderate severity in both groups. One event in the SOK583 group was reported as an SAE. **Reversibility and long-term outcome:** RPE tears may be self-sealing or may require sealing by laser coagulation. **Impact on quality of life:** RPE tears may result in a loss of vision and eventually to legal blindness.
Risk factors and risk groups	Risk factors include nAMD with pigment epithelial detachment and treatment with neovascularizing agents.
Preventability	Due to a lack of clear understanding of the underlying mechanisms of RPE tears, preventive measures are not known. The risk can be reduced by performing a proper intravitreal injection procedure using a correct angle of the needle while injecting.
Impact on the benefit-risk balance of the product	Educational material is provided as an additional risk minimization measure to raise patients' and physicians' awareness on identified and potential risks. This important identified risk was considered in the product benefit-risk assessment, which is positive.
Public health impact	The potential public health impact of this safety concern is considered to be low, due to the low frequency of serious or severe events in clinical trials.

7.3.1.5 Important Identified Risk: Cataract (especially of traumatic origin)

Table 7-10 Important identified risk: Cataract (especially of traumatic origin): Other details

Cataract (especially of traumatic origin)	Details
MedDRA search terms (MedDRA 26.0)	Cataract traumatic; Lenticular injury
Potential mechanisms	Cataracts may occur spontaneously (particularly in the elderly), as a side effect of certain drugs, or following outside influences such as irradiation or mechanical injury (traumatic cataract). During intravitreal injection, a traumatic cataract may be caused when the needle touches the lens.
Evidence source(s) and strength of evidence	This risk was identified in the pivotal studies of the Eylea clinical development program.
Characterization of the risk:	**Frequency:** Cataract (especially of traumatic origin) was not observed in the SOK583 clinical development program. As per the Eylea SmPC (2024), serious ocular adverse reactions in the study eye related to the injection procedure have occurred in less than 1 in 1,900 intravitreal injections with Eylea. Cataract (8%) was among the most frequently observed adverse reaction to Eylea; however, cataract traumatic is listed as rare (≥ 1/10000 to < 1/1000) treatment-emergent ADR. **Severity:** Most events of cataract (especially of traumatic origin) observed for Eylea in the Eylea pivotal studies were of mild or moderate severity; severe events were also reported, but at low frequencies (up to 2%). **Reversibility and long-term outcome:** Cataract development will impair vision and may require surgery to remove lens opacification. **Impact on quality of life:** Patients experiencing (traumatic) cataract will have decreased visual acuity that may require cataract surgery.
Risk factors and risk groups	Cataract is a known adverse drug reaction on treatment with intravitreal corticosteroids. Other risks include aging, trauma, and vitrectomy. Cataract is also associated with inherited retinal disease.
Preventability	As commonly known by treating ophthalmologists, correct placement of the needle and keeping a correct angle during the in intravitreal injection could help preventing a cataract.
Impact on the benefit-risk balance of the product	Educational material is provided as an additional risk minimization measure to raise patients' and physicians' awareness on identified and potential risks. This important identified risk was considered in the product benefit-risk assessment, which is positive.
Public health impact	Patients experiencing (traumatic) cataract may require cataract surgery.

7.3.1.6 Important Potential Risk: Medication errors

Table 7-11 Important potential risk medication errors: Other details

Medication errors	Details
MedDRA search terms (MedDRA 26.0)	Medication errors (SMQ)
Potential mechanisms	Due to excess volumes in the SOK583 vial and PFS, which exceed the recommended net dose of 2 mg aflibercept per injection, injecting more than the approved volume would result in overdose.
Evidence source(s) and strength of evidence	This risk was identified in the pivotal studies of the Eylea clinical development program. No clinically meaningful events of overdose have been reported so far (neither in clinical studies nor in usual care). Nevertheless, it was decided to consider “medication error” a potential risk of treatment, which is, however, completely avoidable by proper adherence to the dosing recommendations.
Characterization of the risk:	**Frequency:** No events of overdose or medication errors were reported in the SOK583 clinical development program. For 1 subject (0.4%) in the SOK583 group, a serious event of “device malfunction” was reported. This however was an event of breast prosthesis impairment and was therefore not considered a relevant medication error event. **Severity:** Medication errors reported for Eylea in the Eylea pivotal studies were of moderate severity. **Reversibility and long-term outcome:** not applicable. **Impact on quality of life:** There is no life-threatening potential when aflibercept is administered intravitreally at a higher dose.
Risk factors and risk groups	No risk groups or risk factors can be identified.
Preventability	Instructions on the correct drug preparation and administration are given in the SmPC and the educational program to minimize the risk of accidental medication errors. The use of single-use vial and PFS limits any potential overdose.
Impact on the benefit-risk balance of the product	Educational material is provided as an additional risk minimization measure to raise patients’ and physicians’ awareness on identified and potential risks. This important identified risk was considered in the product benefit-risk assessment, which is positive.
Public health impact	There is no life-threatening potential when aflibercept is administered by an incorrect route.

7.3.1.7 Important Potential Risk: Off-label use and misuse

Table 7-12 Important potential risk: Off-label use and misuse: Other details

Off-label use and misuse	Details
MedDRA search terms (MedDRA 26.0)	Manual search on master list based on approved indications and population
Potential mechanisms	As with other drugs, aflibercept might be intentionally used other than recommended, or in clinical conditions outside the approved indications.
Evidence source(s) and strength of evidence	This risk was identified in the pivotal studies of the Eylea clinical development program.
Characterization of the risk:	**Frequency:** Off-label use or misuse was not reported in the SOK583 clinical development program. With Eylea, off-label use or misuse was not reported in Eylea clinical studies, but in postmarketing surveillance at a low frequency. **Severity:** Not applicable as no such event was reported during the Eylea clinical development program and severity data were not collected in postmarketing. **Reversibility and long-term outcome:** not applicable. **Impact on quality of life:** not applicable.
Risk factors and risk groups	No risk groups or risk factors can be identified.
Preventability	Intentional misuse is difficult to prevent. However, there is no known dependence potential of aflibercept.
Impact on the benefit-risk balance of the product	Educational material is provided as an additional risk minimization measure to raise patients' and physicians' awareness on identified and potential risks. This important identified risk was considered in the product benefit-risk assessment, which is positive.
Public health impact	Not applicable

7.3.1.8 Important Potential Risk: Embryo-fetotoxicity

Table 7-13 Important potential risk: Embryo-fetotoxicity: Other details

Embryo-fetotoxicity	Details
MedDRA search terms (MedDRA 26.0)	Pregnancy and neonatal topics (SMQ)
Potential mechanisms	During the Eylea development program, an effect of aflibercept on intrauterine development was shown in embryo-fetal development studies in pregnant rabbits.
Evidence source(s) and strength of evidence	This risk was identified in the pivotal studies of the Eylea clinical development program.
Characterization of the risk:	**Frequency:** Pregnancies were not reported in the SOK583 clinical development program. **Severity:** Few pregnancy cases were reported for Eylea in clinical studies and in postmarketing. They did not give any rise to assume that treatment with Eylea might be associated with relevant embryo-fetotoxic effects.

Embryo-fetotoxicity	Details
	Reversibility and long-term outcome: not applicable. **Impact on quality of life:** Based on currently available nonclinical data with Eylea, no individual impact in terms of risk to the treated population is apparent.
Risk factors and risk groups	Women of child-bearing potential are at risk.
Preventability	Although the systemic exposure after ocular administration is very low, aflibercept should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus.
Impact on the benefit-risk balance of the product	Educational material is provided as an additional risk minimization measure to raise patients' and physicians' awareness on identified and potential risks. This important identified risk was considered in the product benefit-risk assessment, which is positive.
Public health impact	Based on currently available nonclinical data with Eylea, no public health impact in terms of risk to the treated population is apparent.

7.3.2 SVII.3.2. Presentation of the missing information (not applicable)

ROP in preterm infants has not been claimed for SOK583. The missing information listed for Eylea "Long-term safety of aflibercept in preterm infants with ROP" is therefore not applicable.

The 8 mg aflibercept dose has not been claimed for SOK583. The missing information listed for Eylea "Exposure with bilateral 8 mg aflibercept therapy" is therefore not applicable.

8 Part II: Module SVIII - Summary of the safety concerns

Table 8-1 Table Part II SVIII.1: Summary of safety concerns

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

9 Part III: Pharmacovigilance plan (including post-authorization safety studies)

9.1 III.1 Routine pharmacovigilance activities

9.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

Specific adverse reaction follow-up checklists will be used to collect further data to help further characterize and/or closely monitor each of the respective safety concerns specified in the table below. The follow-up checklists are provided in Annex 4.

Table 9-1 List of specific adverse reaction follow-up checklists

Form	Safety concern	Purpose
Endophthalmitis and intraocular inflammation (IOI) following the use of Sandoz aflibercept	Endophthalmitis (likely infectious origin) Intraocular inflammation	To gain more knowledge about the 2 risks in patients treated with SOK583 in the post-marketing environment
Intraocular pressure (IOP) increase following the use of Sandoz aflibercept pre-filled syringe (PFS) 0.05 mL containing 2 mg aflibercept	Transient intraocular pressure increase	To gain more knowledge about this risk in patients treated with SOK583 pre-filled syringes in the post-marketing environment

9.2 III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are proposed for SOK583. This section is therefore not applicable.

9.3 III.3 Summary Table of additional pharmacovigilance activities

No additional pharmacovigilance activities are proposed for SOK583. This section is therefore not applicable.

10 Part IV: Plans for post-authorization efficacy studies

Not applicable

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

Risk Minimization Plan

11.1 V.1 Routine risk minimization measures

Table 11-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Endophthalmitis (likely infectious origin)	**Routine risk communication** SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 2, 3, and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** A comprehensive description of the injection procedure (including short-term follow-up) is provided in SmPC section 4.2 Examples of symptoms indicative of endophthalmitis are provided in SmPC section 4.2 and PL section 2 Use of proper aseptic injection techniques is mandated in SmPC section 4.4 and PL section 3 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections.
Intraocular inflammation	**Routine risk communication** SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 2, 3, and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** A comprehensive description of the injection procedure (including short-term follow-up) is provided in SmPC section 4.2 Examples of symptoms indicative of intraocular infection are provided in SmPC section 4.2 and PL section 2 Use of proper aseptic injection techniques is mandated in SmPC section 4.4 and PL section 3 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections.
Transient intraocular pressure increase	**Routine risk communication** SmPC sections 4.2, 4.4, 4.8, and 4.9 PL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Monitoring of intraocular pressure is recommended in SmPC section 4.2 and SmPC section 4.9 The availability of sterile equipment for paracentesis is recommended in Section 4.2

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information: Medicinal product 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** SmPC sections 4.4 and 4.8 PL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Cautions in case of patients with risk factors retinal pigment epithelial tears are recommended in SmPC section 4.4 and PL section 2 **Other routine risk minimization measures beyond the Product Information:** Medicinal product 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 sections 4.2, 4.4, and 4.8 PL sections 2, 3, and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** A comprehensive description of the injection procedure (including short-term follow-up) is provided in SmPC section 4.2 Instructions to patients to have any symptoms indicative of cataract diagnosed and treated without delay or as soon as possible are included in SmPC section 4.4 and PL section 2 Use of proper aseptic injection techniques is mandated in SmPC section 4.4 and PL section 3 **Other routine risk minimization measures beyond the Product Information:** Medicinal product 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 sections 4.2, 4.9, and 6.6 PL sections 1 and 3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** A detailed verbal instructions on how to use the vial/PFS is provided in SmPC section 4.2 and PL section ‘information intended for HCPs only’ Monitoring of intraocular pressure in case of an overdose is recommended in SmPC section 4.9 A detailed and illustrated instruction on how to use the PFS is provided in SmPC section 6.6 and PL section ‘information intended for HCPs only’ **Other routine risk minimization measures beyond the Product Information:** Medicinal product 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** SmPC sections 4.1, 4.3, 4.4, and 4.6

Safety concern	Routine risk minimization activities
	PL sections 1, 2, and 3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Indications of aflibercept are listed in SmPC section 4.1 Contraindications are listed in SmPC Section 4.3 and PL section 2 Conditions in which treatment should be withheld/discontinued/not recommended are included in SmPC section 4.4 and PL section 2 Conditions of use in pregnancy and breastfeeding are included in SmPC section 4.6 and PL section 2 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections.
Embryo-fetotoxicity	**Routine risk communication** SmPC sections 4.4, 4.6, and 5.3 PL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** A recommendation not to use aflibercept during pregnancy is included in SmPC section 4.4 and PL section 2 The use of effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept is mandated in SmPC section 4.6 and PL section 2 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections.

11.2 V.2 Additional Risk minimization measures

Educational materials

Objectives:

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

Generally, the educational material covers the indications nAMD, CRVO, BRVO, myopic CNV, and DME.

The educational material for healthcare professionals include highlighted information regarding treatment of women of child-bearing potential, information on the injection procedure with respect to unnecessary dilation of the eye, with the need for vision and intraocular pressure evaluation after the injection as well as potential for medication misuse, particularly re-use of the vial (see Section 9 Part III).

Rationale for the additional risk minimization activity:

To inform patients and physicians about risks in order to minimize their occurrence and consequences in routine care. Educational material also includes guidance on the intravitreal injection procedure to re-train physicians in order to minimize injection-related adverse reactions.

The following risks are addressed in the educational material:

- 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-fetotoxicity

Target audience and planned distribution path:

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

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

Routine pharmacovigilance activities; AE reports will be reviewed on an ongoing basis and appropriate action taken as needed.

Outcome indicator: Frequency and severity of AEs related to relevant risks.

Removal of additional risk minimization activities

Not applicable

11.3 V.3 Summary of risk minimization measures

Table 11-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Endophthalmitis (likely infectious origin)	Routine risk minimization measures: SmPC sections 4.2, 4.3, and 4.8 SmPC section 4.4 where the use of proper aseptic injection techniques is mandated PL sections 2, 3, and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide and video; in addition, patient guide “Your guide to Afqlir”, and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Adverse reaction follow-up checklist Additional pharmacovigilance activities: None
Intraocular inflammation	Routine risk minimization measures: SmPC sections 4.2, 4.3, and 4.8 SmPC section 4.4 where the use of proper aseptic injection techniques is mandated PL sections 2, 3, and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide and video; in addition, patient guide “Your guide to Afqlir”, and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Adverse reaction follow-up checklist Additional pharmacovigilance activities: None
Transient intraocular pressure increase	Routine risk minimization measures: SmPC section 4.2 where the availability of sterile equipment for paracentesis is recommended	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Adverse reaction follow-up checklist

Safety concern	Risk minimization measures	Pharmacovigilance activities
	SmPC sections 4.4, 4.8, and 4.9 PL sections 2 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide and video; in addition, patient guide “Your guide to Afqlir”, and its audio version).	Additional pharmacovigilance activities: None
Retinal pigment epithelial tears	Routine risk minimization measures: SmPC section 4.4 where cautions in case of patients with risk factors retinal pigment epithelial tears are recommended SmPC section 4.8 PL sections 2 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide and video; in addition, patient guide “Your guide to Afqlir”, and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Cataract (especially of traumatic origin)	Routine risk minimization measures: SmPC sections 4.2 and 4.8 SmPC section 4.4 where the use of proper aseptic injection techniques is mandated PL sections 2, 3, and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide and video; in addition, patient guide “Your guide to Afqlir”, and its audio version).	
Medication errors	Routine risk minimization measures: SmPC sections 4.2, 4.9, and 6.6 PL sections 1 and 3 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide and video; in addition, patient guide “Your guide to Afqlir”, and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Off-label use and misuse	Routine risk minimization measures: SmPC sections 4.1, 4.3, 4.4, and 4.6 PL sections 1, 2, and 3 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide and video; in addition, patient guide “Your guide to Afqlir”, and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Embryo-fetotoxicity	Routine risk minimization measures: SmPC sections 4.4, 4.6, and 5.3 PL section 2 Other routine risk minimization measures beyond the Product Information:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide and video; in addition, patient guide “Your guide to Afqlir”, and its audio version).	None

12 Part VI: Summary of the risk management plan for Afqlir (aflibercept)

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

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

This summary of the RMP for Afqlir 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 Afqlir's RMP.

12.1 I. The medicine and what it is used for

Afqlir is authorised for the treatment of neovascular (wet) age-related macular degeneration (nAMD), 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 (myopic CNV) (see SmPC for the full indication). It contains aflibercept as the active substance and it is given by intravitreal injection.

Further information about the evaluation of Afqlir's benefits can be found in Afqlir's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.eu/medicines/human/EPAR/afqlir.

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

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The 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 minimize its risks.

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

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

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

12.2.1 II.A List of important risks and missing information

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

Table 12-1 List of important risks and missing information

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-fetotoxicity
Missing information	None

12.2.2 II.B Summary of important risks

Table 12-2 Important identified risk: Endophthalmitis (likely infectious origin)

Evidence for linking the risk to the medicine	This risk was identified in the pivotal studies of the Eylea clinical development program.
Risk factors and risk groups	Risk factors include improper aseptic injection technique, which increases the risk of intraocular infection such as endophthalmitis.
Risk minimization measures	Routine risk minimization measures SmPC sections 4.2, 4.3, and 4.8 SmPC section 4.4 where the use of proper aseptic injection techniques is mandated. PL sections 2, 3, and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and

	potential risks (prescriber guide and video; in addition, patient guide "Your guide to Afqlir", and its audio version).

Table 12-3 Important identified risk: Intraocular inflammation

Evidence for linking the risk to the medicine	This risk was identified in the pivotal studies of the Eylea clinical development program.
Risk factors and risk groups	Intraocular inflammation is a known risk of intravitreal injections of anti-VEGFs and other intravitreal applied drugs. Among the factors discussed to contribute to this risk are intravitreal anti-VEGF therapies, silicon oil from syringes, or immune reactions.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.3, and 4.8 SmPC section 4.4 where the use of proper aseptic injection techniques is mandated. PL sections 2, 3, and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide and video; in addition, patient guide "Your guide to Afqlir", and its audio version).

Table 12-4 Important identified risk: Transient intraocular pressure increase

Evidence for linking the risk to the medicine	This risk was identified in the pivotal studies of the Eylea clinical development program.
Risk factors and risk groups	Transient intraocular pressure increase following intravitreal injection is a well-known side effect of any intravitreal administration of liquids used for drug dissolution. However, this condition is limited and usually resolved once the surplus fluid has been resorbed from the inner eye.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.2 where the availability of sterile equipment for paracentesis is recommended. SmPC sections 4.4, 4.8, and 4.9 PL sections 2 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide and video; in addition, patient guide "Your guide to Afqlir", and its audio version).

Table 12-5 Important identified risk: Retinal pigment epithelial tears

Evidence for linking the risk to the medicine	This risk was identified in the pivotal studies of the Eylea clinical development program.
Risk factors and risk groups	Risk factors include nAMD with pigment epithelial detachment and treatment with neovascularizing agents.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 where cautions in case of patients with risk factors retinal pigment epithelial tears are recommended. SmPC section 4.8 PL sections 2 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide and video; in addition, patient guide “Your guide to Afqlir”, and its audio version).

Table 12-6 Important identified risk: Cataract (especially of traumatic origin)

Evidence for linking the risk to the medicine	This risk was identified in the pivotal studies of the Eylea clinical development program.
Risk factors and risk groups	Cataract is a known side effect of intravitreal corticosteroids. Other risks include aging, trauma, and vitrectomy. Cataract is also associated with inherited retinal disease.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2 and 4.8 SmPC section 4.4 where the use of proper aseptic injection techniques is mandated. PL sections 2, 3, and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide and video; in addition, patient guide “Your guide to Afqlir”, and its audio version).

Table 12-7 Important potential risk: Medication errors

Evidence for linking the risk to the medicine	This risk was identified in the pivotal studies of the Eylea clinical development program. No clinically meaningful events of overdose have been reported so far (neither in clinical studies nor in usual care). Nevertheless, it was decided to consider “medication error” a potential risk of treatment, which is, however, completely avoidable by proper adherence to the dosing recommendations.

Risk factors and risk groups	No risk groups or risk factors can be identified.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.9, and 6.6 PL sections 1 and 3 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide and video; in addition, patient guide “Your guide to Afqlir”, and its audio version).

Table 12-8 Important potential risk: Off-label use and misuse

Evidence for linking the risk to the medicine	This risk was identified in the pivotal studies of the Eylea clinical development program.
Risk factors and risk groups	No risk groups or risk factors can be identified.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.1, 4.3, 4.4, and 4.6 PL sections 1, 2, and 3 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide and video; in addition, patient guide “Your guide to Afqlir”, and its audio version).

Table 12-9 Important potential risk: Embryo-fetotoxicity

Evidence for linking the risk to the medicine	This risk was identified in the pivotal studies of the Eylea clinical development program.
Risk factors and risk groups	Women of child-bearing potential are at risk.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4, 4.6, and 5.3 PL section 2 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures:

	Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide and video; in addition, patient guide "Your guide to Afqlir", and its audio version).

12.2.3 II.C Post-authorization development plan

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

There are no studies which are conditions of the marketing authorization or specific obligation of Afqlir.

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

There are no studies required for Afqlir.

13 Part VII: Annexes

Table of contents

Annex 4 - Specific adverse drug reaction follow-up checklists

Endophthalmitis and intraocular inflammation

Targeted Follow-up Checklist Endophthalmitis and intraocular inflammation (IOI) following the use of Sandoz aflibercept (version 1.1, dated 19-Feb-2024)

SECTION I - REFERENCE ID (as available):			
SANDOZ CASE ID:	**STUDY ID:**	**PATIENT ID:**	
SECTION II – REPORTER/ PATIENT INFORMATION:			
REPORTER: ☐ **Physician:** ☐ **Nurse:** ☐ **Other {specify}:** _____			
REPORTER CONTACT INFORMATION:			
Name:			
Institution/Practice Name:			
Phone:		**Fax:**	
Address:			
Email:			
PATIENT INFORMATION:			
Age (Years): **{at event onset}**	**Gender: Male: Female:**	**Weight: Unit (kg/lbs):**	**Height: Unit(kg/lbs):**
SECTION III – PRODUCT INFORMATION (Sandoz aflibercept):			
Therapy date(dd/mm/yyyy): ☐ **Ongoing**			
Indication:		**Number of Sandoz aflibercept doses before the event:**	
☐ **Eye injected/dose**: OS ☐ ☐ 2mg OD ☐ ☐ 2mg			
If both eyes were injected, indicate if the same vial/ PFS was used: ☐ **Yes** ☐ **No If no, please provide batch number per eye: OS**_____ **OD**_____			
Lot/Batch Number:			
Was the same vial used for more than one patient? ☐ **Yes** ☐ **No** **If yes, did the event occur in other patients?** ☐ **Yes** ☐ **No** **If yes, how many**_____			
Was the vial aliquoted in several syringes? ☐ **Yes** ☐ **No** **Was the vial multi-punctured?** ☐ **Yes** ☐ **No**			
Was the supplied filter needle used? ☐ **Yes** ☐ **No** ☐ **Unknown**			

Date and time of injection preparation: (DD/MMM/YYYY; hh:mm):
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? ☐ **Offsite pharmacy** ☐ **on site pharmacy** ☐ **Treatment/examination room**
If prepared in pharmacy, provide the name and contact details:
How many hours did the prepared syringe stay at room temperature prior to administration? _____

SECTION IV – ADVERSE EVENT INFORMATION

Event (*as reported term*) ☐**OS** ☐**OD** ☐**OU**	**Start Date/Time:** (*dd/mm/yyyy/hr:mm*)	**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):**

IF STOP DATE IS UNKNOWN, PROVIDE THE APPROXIMATE EVENT DURATION (DAYS):
IF AE RESOLVED/RESOLVING DID THE VISUAL ACUITY RECOVER TO: ☐ **Same level before AE started** ☐ **Or it is worse**
CLINICAL PRESENTATION:

TREATMENT OF ADVERSE EVENT

Treatment provided: ☐ **Yes** ☐ **No** **If yes, specify ⟹**	☐ **Antibiotics:**	☐ **Steroids (regimen details):**	☐ **Surgery (Vitrectomy) date:**	☐ **Unknown**

☐ **Culture taken on:** **From** ☐**OS** ☐**OD** ☐**OU** ☐ **Culture not taken / Unknown**	☐ **Positive for:** ☐**OS** ☐ **OD** ☐ **OU**	☐ **Negative for:** ☐ **OS** ☐ **OD** ☐ **OU**

REPORTER CAUSALITY COMMENT:		
The event is considered: ☐ **Related to Sandoz aflibercept** ☐ **Related to intravitreal injection procedure** ☐ **Not related to Sandoz aflibercept/ Intravitreal injection procedure**		
Alternative explanation (e.g. Underlying disease/condition predisposing to the event):		
ACTION TAKEN WITH PRODUCT		
	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**		
☐ **Unknown**	**N/A**	**N/A**
Did the event abate/stop after treatment stopped? ☐ **Yes** ☐ **No** ☐ **Unknown**		**Did the event occur upon resuming treatment?** ☐ **Yes** ☐ **No** ☐ **Unknown**

SECTION IV- RELEVANT CLINICAL SYMPTOMS (*to AE of interest*) Please indicate which eye was affected		
Symptoms	**Start date**	**Stop date**
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 events*)			
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*)			
Cause of death: ***(if selected outcome was fatal)***	***Date of death:***	***Autopsy done:***	***Autopsy details:*** ***Continue with section IV***

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

Transient intraocular pressure increase

Targeted Follow-up Checklist for Intraocular pressure (IOP) increase following the use of Sandoz aflibercept pre-filled syringe (PFS) 0.05 mL containing 2 mg aflibercept (version 1.0, dated 29-Feb-2024)

REPORTER INFORMATION			
REPORTER: ☐ Physician: ☐Nurse: ☐ Other {specify}: _____			
Name:			
Institution/Practice Name:			
Phone:		Fax:	
Address:			
Email:			
PATIENT INFORMATION			
Initials *(leave empty for study participants)*:	Age (Years): {at event onset}	Gender: Male: ☐ Female: ☐	
PRODUCT INFORMATION (Sandoz aflibercept vial)			
Therapy date(dd/mm/yyyy):		☐ Ongoing	
Indication:			Number of Sandoz aflibercept doses before the event:
☐ Eye injected/dose:	OS ☐ 2mg OD ☐ 2mg	PFS batch number (s): Date of expiry *(DD/MM/YYYY)*: - -/- -/ - - - -	
ADVERSE EVENT INFORMATION			
Event [*Intraocular pressure (IOP) increase]* ☐ OS ☐ OD	Event start Date/Time: (*dd/mm/yyyy/hr:mm*)		Last injection date before event onset:
Was IOP value measured pre-injection: ☐No, ☐Yes, if yes, please provide: • IOP value(s) (mmHg): • Time/minutes pre-injection and date: • Method:			
Was IOP value measured post-injection: ☐No, ☐ Yes, if yes, please provide: • IOP value(s) (mmHg): • Time/minutes post-injection and date: • Method:			
How long did the increased IOP last after the injection?			
Outcome of IOP increase event	☐ Recovering/ resolving ☐ Recovered/ resolved without sequelae. ☐ Recovered/ resolved with sequelae, please provide sequelae details: ☐ Not recovered/ not resolved ☐ Unknown		

Did the patient experience any other clinical sign or symptom in the context of post-injection IOP increase? ☐No, ☐Yes, if yes, which other medical conditions/ symptoms were experienced and what is the outcome of the events? Please indicate outcome in the box to the right.	☐ Recovering/ resolving (event/s:_____) ☐ Recovered/ resolved without sequelae (event/s:_____) ☐ Recovered/ resolved with sequelae, please provide sequelae details (event/s: _____) ☐ Not recovered/ not resolved (event/s: _____) ☐ Unknown (event/s: _____) ☐ Not applicable:
Was post-injection fundoscopy performed? ☐ No, ☐ Yes, if yes, please provide results and post injection timing:	

TREATMENT OF ADVERSE EVENT

Was any intervention done to treat increased IOP? ☐ No ☐ Yes If yes, please specify measures taken including date and time:	
Does the patient have a history of glaucoma, ocular hypertension or glaucoma surgery or take anti-glaucoma medication in the injected or the fellow eye? ☐ No ☐ Yes If yes, please provide details:	☐ OS ☐ OD ☐ OU Details:
Has the patient's anterior chamber angle been assessed in the eye(s) with IOP increase? ☐ No, ☐ Yes, if Yes, please provide result details, date: timing (pre or post injection):	By which method? Is the angle open, narrow or closed? ☐ OS ☐ OD Details:
Did the patient use corticosteroids or any other medication, that could increase IOP? ☐ No, ☐ Yes, if Yes, please specify the drug/s and indications:	

Does the patient have any of the following comorbid conditions (please check all that apply)?
□ diabetes □ high blood pressure □ low blood pressure □ retinal ischemia □CRAO □ BRAO □ eye trauma □ eye surgeries □ myopia □ pseudo exfoliation syndrome □ pigment dispersion syndrome □ cornea arcus present, details
……

PFS details

Who prepared the Sandoz aflibercept injection (e.g. physician, nurse, other)?
Was the individual specifically trained on the Sandoz aflibercept PFS? No ☐ Yes ☐

Who conducted the Eylea injection with the PFS (e.g., physician, nurse)?
Was the individual specifically trained on the Sandoz aflibercept PFS? No ☐ Yes ☐

Was the 30G needle used for injection? Yes ☐ No ☐; If no which needle size was used?
Brand of injection needle, if known:

Were all bubbles eliminated/ expelled, excess drug expelled, and the plunger correctly adjusted to the dose line before injection (moving the base of plunger dome (not the tip) to the dosing line)? Yes ☐ No ☐ If No, please provide details:	
Was there any difficulty in preparing the PFS according to the instructions prior to the injection? ☐ No, ☐ Yes, if Yes, please provide explain:	
Was there any physical or handling abnormality observed with the syringe? ☐ No, ☐ Yes, if Yes, please specify:	
For this event, did you see any foreign particles, discoloration or change in physical appearance of the Sandoz aflibercept solution? ☐ No, ☐ Yes, if yes, provide details:	
For this event, have you injected, or attempted to inject the residual volume which remained in the syringe after completion of injection? ☐ No, ☐ Yes, if yes, please provide details:	

Other anti-VEGF treatment

Did the patient have previous intravitreal injections? ☐ No, ☐ Yes; if Yes, please fill adjacent columns to the right	Sandoz: ☐ Vial ☐ PFS Other intravitreal injections ☐	Was IOP increase also observed after previous intraocular injections? ☐ No ☐ Yes, details please:
Further notes *(free text)*:		

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Draft key messages of the additional risk minimization measures

Prior to the launch of Afqlir in each Member State, the Marketing Authorization Holder (MAH) must agree about the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.

The educational program is aimed at patients and physicians to inform about the important risks of Afqlir in order to minimize their occurrence and consequences in routine care.

The MAH shall ensure that in each Member State where Afqlir is marketed, all ophthalmological clinics where Afqlir is expected to be used are provided with the following educational package:

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

Physician information included in the educational package:

- Techniques for the intravitreal injection including use of a 30 G needle, and angle of injection
- The pre-filled syringe and the vial are for single use only
- The need to expel excess volume of the syringe before injecting Afqlir 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 Afqlir

The patient information pack of the educational material includes a patient information guide and an audio-recording medium that contain following key elements:

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