EU Risk Management Plan for Afiveg 40 mg/mL solution for injection in pre-filled syringe & Afiveg 40 mg/mL solution for injection (Aflibercept)

RMP version to be assessed as part of this application:

RMP Version number: 0.2

Data lock point for this RMP: 2025-May-08

Date of final sign off: 2025-May-08

Rationale for submitting an updated RMP: RMP was updated to align with RMP V1.1 of Advanz Pharma Limited (date of final sign off: 06-Feb-2025).

Summary of significant changes in this RMP: Implementation of updated invented name; minor corrections and formal changes in Part II; inclusion of additional risk minimization measures in Part V (V.2 and V.3), Part VI (II.B) and Annex 6 to align with the reference product Eylea; update of Annex 7 and 8.

Other RMP versions under evaluation:

RMP Version number: N/A

Submitted on: N/A

Procedure number: N/A

Details of the currently approved RMP:

Version number: N/A

Approved with procedure: N/A

Date of approval (opinion date): N/A

QPPV Name: Dr. Andreas Iwanowitsch

QPPV Signature:

Table of content

Part I: Product(s) Overview

Table1-1: Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Aflibercept
Pharmacotherapeutic group(s) (ATC Code)	Ophthalmologicals, Antineovascularisation agents ATC code: S01LA05
Marketing Authorisation Applicant	STADA Arzneimittel AG
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	Afiveg 40 mg/mL solution for injection in pre-filled syringe Afiveg 40 mg/mL solution for injection
Marketing authorisation procedure	Centralised Procedure (EMEA/H/C/6761)
Brief description of the product	Chemical class: Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1. Aflibercept is a specific blocker that binds and inactivates vascular endothelial growth factor (VEGF) and the related molecule, placental growth factor (PIGF).
	Summary of mode of action: It is designed to interfere with the increase in vascular permeability and growth of pathological new blood vessels that lead to retinal oedema, ischemia and haemorrhage in diseases accompanied by ocular neovascularization.
	Important information about its composition: Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.
Hyperlink to the Product Information	The product information is included in Module 1.3.1 of the eCTD sequence.

Indication(s) in the EEA	Current: Afiveg is indicated for adults for the treatment of • neovascular (wet) age-related macular degeneration (AMD), • visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), • visual impairment due to diabetic macular oedema (DME), • visual impairment due to myopic choroidal neovascularisation (myopic CNV).
	Proposed (if applicable): not applicable.
Dosage in the EEA	Current: Afiveg is for intravitreal injection only. Afiveg must only be administered by a qualified physician experienced in administering intravitreal injections. <u>Posology</u> *wet AMD* The recommended dose for Afiveg is 2 mg aflibercept, equivalent to 0.05 mL. Afiveg treatment is initiated with one injection per month for three consecutive doses. The treatment interval is then extended to two months. *Macular oedema secondary to RVO (branch RVO or central RVO)* The recommended dose for Afiveg is 2 mg aflibercept equivalent to 0.05 mL. After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month. *Diabetic macular oedema* The recommended dose for Afiveg is 2 mg aflibercept equivalent to 0.05 mL. Afiveg treatment is initiated with one injection per month for five consecutive doses, followed by one injection every two months. *Myopic choroidal neovascularisation* The recommended dose for Afiveg is a single intravitreal injection of 2 mg aflibercept equivalent to 0.05 mL. The interval between two doses should not be shorter than one month.
	Proposed (if applicable): not applicable.

Pharmaceutical form(s) and strengths	Current: <u>Afiveg 40 mg/mL solution for injection in pre-filled syringe:</u> 1 mL solution for injection contains 40 mg aflibercept. One pre-filled syringe contains an extractable volume of at least 0.09 mL, equivalent to at least 3.6 mg aflibercept. This provides a usable amount to deliver a single dose of 0.05 mL containing 2 mg aflibercept to adult patients. <u>Afiveg 40 mg/mL solution for injection (in a vial):</u> 1 mL solution for injection contains 40 mg aflibercept. One vial contains an extractable volume of at least 0.1 mL, equivalent to at least 4 mg aflibercept. This provides a usable amount to deliver a single dose of 0.05 mL containing 2 mg aflibercept.
	Proposed (if applicable): not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Afiveg has been developed as a biosimilar to Eylea, containing aflibercept as an active substance. Product name of Afiveg during non-clinical and clinical development was AVT06.

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

Not applicable. Omitted module for biosimilar products.

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

Key safety findings from non-clinical studies	Relevance to human usage
Key issues identified from acute or repeat-dose toxicity studies: Single dose: No single dose toxicity studies of AVT06 (Aflibercept) have been conducted. Repeat-Dose Toxicity Study: Study's findings support the strong comparability between AVT06 and Eylea in cynomolgus monkeys. The study results demonstrated comparable systemic and ocular toxicity profile between AVT06 and Eylea. *In Vitro* Toxicity Study: *In vitro* toxicity study in primary human retinal cells shows low toxicity after exposure to AVT06 and Eylea drug products/vehicles. Reproductive/developmental toxicity: No Reproductive/ developmental toxicity studies of AVT06 have been conducted. Genotoxicity/ Carcinogenicity: No genotoxicity/carcinogenicity studies of AVT06 have been conducted.	None
Safety Pharmacology No studies to evaluate safety pharmacology of AVT06 have been conducted in accordance with the European Medicine Agency (EMA) and Food and Drug Administration (FDA) guidance for development of biosimilar.	No direct impact expected.

Part II: Module SIII - Clinical trial exposure

One (1) company-sponsored clinical trial has been conducted with aflibercept since the Development International Birth Date (DIBD).

Completed study: AVT06-GL-C01
A Randomized, Double-masked, Parallel-group, Multicenter Clinical Study to Evaluate the Efficacy and Safety of AVT06 Compared with EU-Eylea in Subjects with Neovascular (wet) Age-related Macular Degeneration (ALVOEYE)

Table SIII.1: Cumulative subject exposure from completed clinical trials

Treatment	Number of subjects
AVT06	205
Comparator - EU Eylea	205
Total subjects	**410**

Table SIII.2: Duration of exposure to AVT06 from completed clinical trials

Duration	Number of subjects
<1 month	0
1 to ≤ 3 months	205

Table SIII.3: Cumulative subject exposure to AVT06 from completed clinical trials by age

Gender	Number of subjects
<50 years	0
≥50 years	205
Total subjects	**205**

Table SIII.4: Cumulative subject exposure to AVT06 from completed clinical trials by gender

Gender	Number of subjects
Male	102
Female	103
Total subjects	**205**

Table SIII.5: Cumulative subject exposure to AVT06 from completed clinical trials by race

Race	Number of subjects
Asian	34
Black or African American	1
Caucasian/White	154
Japanese	14
Other	2
Total subjects	**205**

Table SIII.6: Cumulative subject exposure to AVT06 from completed clinical trials by ethnicity

Ethnicity	Number of subjects
Hispanic or Latino	36
Non Hispanic or Latino	166
Not reported	3
Total subjects	**205**

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

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

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
Subjects with previous ocular (intraocular and peribulbar) corticosteroids injection/implant within 1 year in the study eye prior to randomization. Topical ocular corticosteroids for 30 or more consecutive days within 90 days prior to randomization in the study eye. Previous therapeutic radiation in the region of the study eye. Any prior ocular treatment, including surgery or another investigational product for neovascular AMD (including anti-VEGF therapy), in the study eye, except dietary supplements or vitamins. Prior vitrectomy or laser surgery of the macula (including photodynamic therapy or focal laser photocoagulation) in the study eye. Any ocular treatment, including surgery or another investigational product for neovascular AMD (including anti-VEGF treatment), in the fellow eye, within 6 months before randomization, except dietary supplements or vitamins. Prior treatment with systemic steroids within 30 days of screening, with the exception of low stable doses of corticosteroids (defined as 10 mg or lower oral prednisolone or equivalent dose used for 90 days or more prior to screening. Treatment with systemic medications known to be toxic to the lens, retina, or optic nerve including (but not limited to) deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, vigabatrin, and ethambutol from the time of screening.	Interference with the evaluation of efficacy and safety data.	No	As per the SmPC, concomitant use of other anti-VEGF (vascular endothelial growth factor): There is no data available on the concomitant use of aflibercept with other anti-VEGF medicinal products (systemic or ocular). No interaction studies have been performed. Adjunctive use of verteporfin photodynamic therapy (PDT) and aflibercept has not been studied, therefore, a safety profile is not established.

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
Aphakia or absence of the posterior capsule in the study eye. Any concurrent macular abnormality other than wet AMD which could affect central vision or the efficacy of the study treatment in the study eye. Significant media opacities, including cataract or inadequate pupil dilatation, which might interfere with visual acuity or assessment of safety in the study eye. History of corneal transplant, corneal dystrophy, or corneal ectasia (such as either keratoconus or keratoglobus) in the study eye.	These findings may interfere with study procedure and interpretation of results. In addition, to maintain feasibility of safety and efficacy assessments, particularly imaging these populations were excluded.	No	Cataract (especially of traumatic origin) is considered as an important identified risk.
History or clinical evidence of uveitis, diabetic retinopathy, diabetic macular oedema, or any other vascular disease affecting the retina, other than neovascular AMD.	To reduce the impact of confounding factors on safety measurements.	No	No safety concern was anticipated.
Active or suspected ocular or periocular infection, within 2 weeks before randomization.	Aflibercept has not been studied in patients with active systemic infections.	No	Use of Aflibercept in patients with active or suspected ocular or periocular infection is contraindicated.
Uncontrolled ocular hypertension (defined as IOP ≥25 mmHg despite treatment with anti- glaucoma medication) at screening and randomization visits in the study eye. History of retinal detachment in the study eye. Any history of macular hole in the study eye.	Aflibercept has not been studied in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with aflibercept in diabetic patients with uncontrolled hypertension.	No	Not considered as relevant for the safety profile. No further warnings or Contraindication have been included.
Known hypersensitivity to aflibercept or its excipients.	Patients with known hypersensitivity to aflibercept or excipients should not use.	No	Use in this population is contraindicated as per the SmPC.

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
Intraocular inflammation.	Patients with any active intraocular inflammation or infection in either eye or history of intraocular inflammation or infection after past intravitreal (IVT) injections with any agent in either eye should not use.	No	Use in this population is contraindicated as per the SmPC. Intraocular inflammation is also considered as an important identified risk.
Retinal pigment epithelial tears.	Criterion to avoid a potential safety bias.	No	Comprehensive wording concerning the risk of retinal pigment epithelial tear (is currently in section 4.4 "Special warnings and precautions for use" and section 4.8 “Undesirable effects” of the SmPC. Retinal pigment epithelial tears are considered as an important identified risk.
Uncontrolled cardiovascular disease including hypertension, heart failure, or clinically significant electrocardiogram (ECG) abnormality, including subjects with QT interval corrected using Fridericia’s formula (QTcF) >480 ms at screening, confirmed by repeat assessment. Acute coronary event or stroke within 6 months before randomization.	There are limited data on safety in treating patients with CRVO, BRVO, DME and myopic CNV who have had a stroke or a mini-stroke (transient ischaemic attack) or a heart attack within the last 6 months.	No	As per SmPC, the systemic use of VEGF inhibitors, substances similar to those contained in Afiveg, is potentially related to the risk of blood clots blocking blood vessels (arterial thromboembolic events) which may lead to heart attack or stroke. There is a theoretical risk of such events following injection

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
			of Aflibercept into the eye. Aflibercept should therefore be given with caution.

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

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

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

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme.
Population with relevant different ethnic origin	Japanese: 27
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme.
Other	N/A

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable since the product is not yet commercialised.

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

Potential for misuse for illegal purposes

Aflibercept is not structurally or pharmacologically related to any drug known to cause abuse or dependence, and it is not expected to have a potential for misuse as a recreational drug.

Part II: Module SVII - Identified and potential risks

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

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

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

The information available for aflibercept has been analysed and those risks not considered important for inclusion in the list of safety concerns in the RMP (along with the reason of not inclusion) are detailed below:

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

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

- Eye disorders: Visual acuity reduced, Vision blurred, Conjunctival haemorrhage, Conjunctival hyperaemia, Ocular hyperaemia, Vitreous haemorrhage, Vitreous floaters, Eye pain, Injection site pain, Injection site haemorrhage, Injection site irritation, Lacrimation increased, Foreign body sensation in eyes, Abnormal sensation in eye, Eyelid irritation, Retinal haemorrhage, Eyelid oedema, Anterior chamber flare, Corneal oedema.

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

- Eye disorders: Detachment of the retinal pigment epithelium, Retinal degeneration, Vitreous detachment, Corneal erosion, Corneal abrasion, Punctate keratitis, Corneal epithelium defect.

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

- Eye disorders: Blindness, Retinal detachment, Retinal tear.

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

Important Identified Risk 1: Endophthalmitis (likely infectious origin)

Endophthalmitis cases have been observed in the clinical trial program of the originator. Endophthalmitis cases (and other cases of intraocular inflammation) have been reported in post-marketing setting of the originator.

The proportion of adult patients exposed to aflibercept who experienced endophthalmitis in the study eye in the clinical studies with the originator was low (range from 0% to 0.9%). Endophthalmitis is regarded as an uncommon ADR. Endophthalmitis cases (and other cases of intraocular inflammation) reported in post-marketing setting are subject to additional follow-up using specific questionnaires.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Important Identified Risk 2: Intraocular inflammation

Intraocular inflammation cases have been observed in the clinical trial program of the originator. Endophthalmitis and other cases of intraocular inflammation have been reported in post-marketing setting of the originator.

The proportion of adult patients exposed to aflibercept who experienced intraocular inflammation in the study eye in the clinical studies with the originator ranged from 0% to 2.6%. Single preferred terms events associated with intraocular inflammation are considered uncommon ADRs (e.g., iritis, uveitis, iridocyclitis) or rare ADRs (vitritis, hypopyon). Endophthalmitis and other cases of intraocular inflammation reported in post-marketing setting are subject to additional follow-up using specific questionnaires.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Important Identified Risk 3: Transient intraocular pressure increase

The proportion of adult patients exposed to aflibercept who experienced an increase in intraocular pressure in the study eye in the clinical studies with the originator ranged from 2.8% to 13.6%, but the vast majority of these events were resolved. Systematic measurements of IOP during the course of the clinical studies with the originator did not indicate a trend towards sustained IOP increase. The single preferred term “Intraocular pressure increased” is considered a common ADR. Transient intraocular pressure increase reported in post- marketing setting are subject to additional follow-up using specific questionnaires.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Important identified Risk 4: Retinal pigment epithelial tears

RPE tear is considered a common ADR. However, the total incidence of RPE tears in the AMD Phase III clinical trials of the originator was in line with the known background incidences from literature and the absence of RPE tear in the clinical studies investigating the non-AMD indications of the originator suggests that RPE tear development caused by IVT treatment with aflibercept is rather unlikely.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

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

The proportion of adult patients exposed to aflibercept who experienced traumatic cataract in the study eye in the clinical studies with the originator ranged from 0% to 2.8%. Various forms of cataract (cortical, nuclear, subcapsular) are considered common ADRs; traumatic cataract is regarded as a rare ADR.

There is currently no evidence that the occurrence of a traumatic cataract is increased on treatment with aflibercept. However, as this might be a hypothetical result of the lens perforation, it has been included as important identified risk.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Important potential risk 1: Medication errors

Medication error is considered a potential risk of treatment, however, this risk is considered as completely avoidable by proper adherence to the dosing recommendations in the SmPC.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Important potential risk 2: Off-label use and misuse

As with other drugs, Afiveg might be intentionally used other than recommended, or in clinical conditions outside the approved indications. Afiveg does not have any dependence potential. Since the clinical experience with Afiveg 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.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Important potential risk 3: 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 IVT-administered anti-VEGF therapies in pregnancy is sparse (single cases reported only) and thus inconclusive, therefore, particular attention is paid to this safety issue. No cases of embryo-fetotoxicity were reported during the clinical development program of the originator; however, pregnant females were excluded from clinical study participation. Current post-marketing surveillance data of the originator do not suggest an increased risk of embryo-fetotoxicity on treatment with aflibercept.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

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

Not applicable, as no European Union Risk Management Plan (EU-RMP) has previously been submitted.

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

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

Important identified risk 1: Endophthalmitis (likely infectious origin)

Potential mechanisms:

The intravitreal injection procedure can implant pathogens into the eye if there is a break in sterile technique. Source of pathogenic agents is in most cases the patient's conjunctival bacterial flora.

Evidence source(s) and strength of evidence:

Endophthalmitis cases have been observed in the clinical trial program of the originator. Endophthalmitis cases (and other cases of intraocular inflammation) have been reported in post-marketing setting of the originator.

The proportion of adult patients exposed to aflibercept who experienced endophthalmitis in the study eye in the clinical studies with the originator was low (range from 0% to 0.9%). Endophthalmitis is regarded as an uncommon ADR. Endophthalmitis cases (and other cases of intraocular inflammation) reported in post-marketing setting are subject to additional follow-up using specific questionnaires.

Characterisation of the risk:

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

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

Risk factors and risk groups:

Improper aseptic technique increases the risk of intraocular inflammation.

Preventability:

The risk of intraocular inflammation, especially if caused by pathogens, cannot be completely excluded, but may be minimized. In the scope of intravitreal injections of drugs for treatment of wet AMD, CRVO, BRVO, myopic CNV, or DME (by which pathogens might be inadvertently carried into the inner eye), it is absolutely crucial to work under strict aseptic and sterile conditions.

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

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

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

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

Important identified risk 2: Intraocular inflammation

Potential mechanisms:

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

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

Evidence source(s) and strength of evidence:

Intraocular inflammation cases have been observed in the clinical trial program of the originator. Endophthalmitis and other cases of intraocular inflammation have been reported in post-marketing setting of the originator.

The proportion of adult patients exposed to aflibercept who experienced intraocular inflammation in the study eye in the clinical studies with the originator ranged from 0% to 2.6%. Single preferred terms events associated with intraocular inflammation are considered uncommon ADRs (e.g., iritis, uveitis, iridocyclitis) or rare ADRs (vitritis, hypopyon). Endophthalmitis and other cases of intraocular inflammation reported in post-marketing setting are subject to additional follow-up using specific questionnaires.

Characterisation of the risk:

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

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

Risk factors and risk groups:

Improper aseptic technique increases the risk of intraocular inflammation.

Preventability:

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

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

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

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

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

Important identified risk 3: Transient intraocular pressure increase

Potential mechanisms:

Transient IOP increase is attributed to an increase in vitreous volume (volume effect).

Evidence source(s) and strength of evidence:

The proportion of adult patients exposed to aflibercept who experienced an increase in intraocular pressure in the study eye in the clinical studies with the originator ranged from 2.8% to 13.6%, but the vast majority of these events were resolved. Systematic measurements of IOP during the course of the clinical studies with the originator did not indicate a trend towards sustained IOP increase. The single preferred term “Intraocular pressure increased” is considered a common ADR. Transient intraocular pressure increase reported in post- marketing setting are subject to additional follow-up using specific questionnaires.

Characterisation of the risk:

Due to the filling of the eye-ball with liquids (i.e., aqueous and vitreous humour), there is an inherent pressure in the eye, which is measured in the same unit as the blood pressure is (i.e., in millimetre Mercury; mmHg). Normal pressure in the inner eye is approximately 10-21 mmHg. Elevated eye pressure is a major risk factor for a condition called "glaucoma", which is characterized by a loss of nerve fibres in the optic nerve with the subsequent risk of blindness. However, many different factors may be responsible for the development of glaucoma, and increased intraocular pressure is not a mandatory prerequisite for the development of glaucoma (e.g., the condition of normal-tension glaucoma is well-known). In the scope of intravitreal injections, it is easily comprehensible that the volume load caused by the application of the drug, which is dissolved in a certain amount of injection liquid, will lead to a transient increase of intraocular pressure at least until the surplus fluid will have been resorbed from the inner eye.

Risk factors and risk groups:

Patients with glaucoma.

Increased intraocular pressure is a known adverse drug reaction on treatment with intravitreal corticosteroids.

Preventability:

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

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

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

Important identified risk 4: Retinal pigment epithelial tear

Potential mechanisms:

Development of RPE tears after anti-VEGF intravitreal injection has been attributed to a decline in intercellular adherence, thereby increasing susceptibility to tearing of the RPE layer.

Evidence source(s) and strength of evidence:

RPE tear is considered a common ADR. However, the total incidence of RPE tears in the AMD Phase III clinical trials of the originator was in line with the known background incidences from literature and the absence of RPE tear in the clinical studies investigating the non-AMD indications of the originator suggests that RPE tear development caused by IVT treatment with aflibercept is rather unlikely.

Characterisation of the risk:

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

Risk factors and risk groups:

Wet AMD with pigment epithelial detachment; treatment of neovascularization.

Preventability:

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

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

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.

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

Potential mechanisms:

Related to IVT procedure.

Evidence source(s) and strength of evidence:

The proportion of adult patients exposed to aflibercept who experienced traumatic cataract in the study eye in the clinical studies with the originator ranged from 0% to 2.8%. Various forms of cataract (cortical, nuclear, subcapsular) are considered common ADRs; traumatic cataract is regarded as a rare ADR.

There is currently no evidence that the occurrence of a traumatic cataract is increased on treatment with aflibercept. However, as this might be a hypothetical result of the lens perforation, it has been included as important identified risk.

Characterisation of the risk:

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

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

Risk factors and risk groups:

Cataract is a known adverse drug reaction on treatment with IVT corticosteroids.

Preventability:

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

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

Patients experiencing (traumatic) cataract may require cataract surgery.

Important potential risk 1: Medication errors

Potential mechanisms:

Not applicable.

Evidence source(s) and strength of evidence:

Two milligram (2 mg) aflibercept is provided in vial or a pre-filled syringe format. In both vial and PFS presentations, excess volume is to be expelled during the priming step before injecting the recommended dose. Thus, injecting the entire volume of the pre-filled syringe/vial would result in overdose. However, this numerical overdose is limited, and the drug will be administered only by qualified physicians (not by patients), and this reduces the risk of inappropriate dosing and administration as well. Proper adherence to the instructions for use when using the PFS/vial is key to avoid overdosing.

Characterisation of the risk:

Not applicable.

Risk factors and risk groups:

Not applicable.

Preventability:

Instructions on the correct drug preparation and administration are given in the SmPC in order to minimize the risk of accidental medication errors.

Proper preparation of the injection with the 2 mg Afiveg PFS and for 2 mg Afiveg vial according to the Instruction for Use is key in mitigating medication error leading to overdose.

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

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

Important potential risk 2: Off-label use and misuse

Potential mechanisms:

Not applicable.

Evidence source(s) and strength of evidence:

As with other drugs, Afiveg might be intentionally used other than recommended, or in clinical conditions outside the approved indications (off-label use). Since the clinical experience with Afiveg in such off-label use will be limited (in particular in terms of efficacy and safety), any case of off-label use will be considered a potential risk. Since Afiveg has no dependence potential, the risk of misuse is regarded as very low.

Characterisation of the risk:

Not applicable.

Risk factors and risk groups:

Not applicable.

Preventability:

As for the majority of possible indications for anti-VEGF therapy approved medications are available, the potential for off-label use is considered minimal.

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

Not applicable.

Important potential risk 3: Embryo-fetotoxicity

Potential mechanisms:

An embryo-fetal toxicity study was performed by the originator in the rabbit with IV dosing of aflibercept at doses which provided systemic exposures over 670-fold higher than that observed with IVT dosing using the clinical dose of 2 mg. The study identified dose-related increases in fetal resorptions, pregnancy disruptions and numerous fetal (external, visceral and skeletal) malformations. These effects were thought to be due to the antiangiogenic effect of aflibercept.

Evidence source(s) and strength of evidence:

Testing of the originator product in animals was performed as a standard part of the development of the originator product. It was noted that originator product given in extremely high doses to animals (by far exceeding the doses which would be given to humans) might have an adverse influence on prenatal development (i.e., during the embryonic or fetal development period; so-called embryo-fetotoxicity). Therefore, embryo-fetotoxicity is regarded as a potential risk of treatment with originator product. However, originator product injected locally and at a dose that is distinctively lower than the exposure in animals under which the critical events were observed.

So far, there is no relevant indication that treatment with originator product might be associated with embryo-fetotoxicity.

Characterisation of the risk:

Not applicable.

Risk factors and risk groups:

Patients at risk are women of childbearing potential.

Preventability:

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

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

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

SVII.3.2. Presentation of the missing information

Not applicable. There is no missing information for aflibercept.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

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

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities include routine follow-up of all adverse drug reaction reports lacking information on the batch number and/or brand name. Therefore, all appropriate measures are taken for biological medicinal products to clearly identify the names of the products and batch numbers.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific Adverse Reaction Follow-up Questionnaires

In order to optimize the data collection for defined medical conditions, specific follow-up questionnaires will be used:

- Endophthalmitis and Intraocular inflammation (IOI)
- Intraocular pressure (IOP) with pre-filled syringes of Afiveg

The forms are provided in the Annex 4 of the RMP.

Other Forms of Routine Pharmacovigilance Activities for safety concerns

No other forms of Routine Pharmacovigilance Activities beyond adverse reaction reporting, signal detection and the ones described above will be implemented for Afiveg.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities will be conducted.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable as no post-authorisation efficacy studies are planned.

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

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

Safety concern	Routine risk minimisation activities
Endophthalmitis (likely infectious origin)	Routine risk communication: SmPC sections 4.2, 4.3, 4.4 and 4.8. Patient Information Leaflet (PIL) sections 2, 3 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 of the SmPC states that following intravitreal injection, adult patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay. Section 4.3 of the SmPC states that Afiveg is contraindicated in active or suspected ocular or periocular infection and in active severe intraocular inflammation Section 4.4 of the SmPC states that intravitreal injections, including those with Afiveg, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see section 4.8). Proper aseptic injection techniques must always be used when administering Afiveg. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Adult patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay. Section 4.8 of the SmPC specifies serious ocular adverse reactions related to the injection procedure with the use of Afiveg. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2, 3 and 4. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Intraocular inflammation	Routine risk communication: SmPC sections 4.2, 4.3, 4.4 and 4.8. PIL sections 2, 3 and 4.

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 of the SmPC states that intravitreal injections must be carried out by a qualified physician experienced in administering intravitreal injections. Adequate anaesthesia and asepsis, including topical broad-spectrum microbicide, have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended. Section 4.3 of the SmPC states that Afiveg is contraindicated in active or suspected ocular or periocular infection and in active severe intraocular inflammation. Section 4.4 of the SmPC states that intravitreal injections, including those with Afiveg, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see SmPC section 4.8). Proper aseptic injection techniques must always be used when administering Afiveg. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Patients should be instructed to report any signs or symptoms of intraocular inflammation, e.g. pain, photophobia, or redness, which may be a clinical sign attributable to hypersensitivity. Section 4.8 of the SmPC specifies serious ocular adverse reactions related to the injection procedure with the use of Afiveg. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2, 3 and 4. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Transient intraocular pressure increase	Routine risk communication: SmPC sections 4.2, 4.4, 4.8 and 4.9. PIL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 of the SmPC states that immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available. Section 4.4 of the SmPC states that increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with Afiveg (see SmPC section 4.8). Special precaution is

Safety concern	Routine risk minimisation activities
	needed in patients with poorly controlled glaucoma (do not inject Afiveg while the intraocular pressure is ≥ 30 mmHg). In all cases, both the intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately. Section 4.8 of the SmPC specifies serious ocular adverse reactions related to the injection procedure with the use of Afiveg. Section 4.9 of the SmPC states that overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdose, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Retinal pigment epithelial tears	Routine risk communication: SmPC sections 4.4 and 4.8. PIL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 of the SmPC states that risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD, include a large and/or high pigment epithelial retinal detachment. When initiating aflibercept therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears. Section 4.8 of the SmPC specifies adverse reactions associated with the use of Afiveg including Retinal pigment epithelial tears. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.

Safety concern	Routine risk minimisation activities
Cataract (especially of traumatic origin)	Routine risk communication: SmPC sections 4.2, 4.4 and 4.8. PIL sections 2, 3 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 of the SmPC states that intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. In general, adequate anaesthesia and asepsis, including topical broad spectrum microbicide (e.g. povidone iodine applied to the periocular skin, eyelid and ocular surface), have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended. Section 4.4 of the SmPC states that intravitreal injections, including those with aflibercept, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Proper aseptic injection techniques must always be used when administering aflibercept. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Adult patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay. Section 4.8 of the SmPC specifies serious ocular adverse reactions associated with the use of Afiveg including cataract. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2, 3 and 4. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Medication errors	Routine risk communication: SmPC sections 4.2, 4.9 and 6.6. PIL sections 1 and 3. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 of the SmPC states that pre-filled syringe contains more than the recommended dose of 2 mg aflibercept. The extractable volume of the syringe is the amount that can be expelled from the syringe and is not to be used in total. For the Afiveg pre-filled syringe, the extractable volume is at least 0.09 mL. The excess volume must be expelled before injecting the recommended dose. Injecting the entire volume of the pre-filled syringe could result in overdose. Section 4.9 of the SmPC states that in case of overdose, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

Safety concern	Routine risk minimisation activities
	SmPC Section 6.6 and Package Leaflet section "The following information is intended for healthcare professionals only" provide instruction for the use of the pre-filled syringe. In order to inform patients of this risk, corresponding text is also present in the PIL sections 1 and 3. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Off-label use and misuse	Routine risk communication: SmPC sections 4.1, 4.3, 4.4 and 4.6. PIL sections 1, 2 and 3. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.1 lists all therapeutic indications for Afiveg. Section 4.3 of the SmPC states that Afiveg is contraindicated in case of hypersensitivity to the active substance aflibercept or to any of the excipients listed in Section 6.1. Aflibercept is contraindicated in active or suspected ocular or periocular infection and also in active severe intraocular inflammation. Section 4.4 of the SmPC lists all conditions in which the treatment should be withheld, discontinued or not-recommended. Section 4.6 of the SmPC states that Afiveg. should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept. In order to inform patients of this risk, corresponding text is also present in the PIL sections 1, 2 and 3. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Embryo-fetotoxicity	Routine risk communication: SmPC sections 4.4, 4.6 and 5.3. PIL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 of the SmPC states that women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of Afiveg.

Safety concern	Routine risk minimisation activities
	Section 4.6 of the SmPC states that Afiveg should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of Afiveg. Section 5.3 of the SmPC states that effect of aflibercept on intrauterine development was shown in embryo-foetal development studies in rabbits. In order to inform patients of this risk, corresponding text is also present in PIL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.

V.2. Additional Risk Minimisation Measures

Educational Material:

Besides routine risk minimization activities (SmPC and patient information), additional risk minimisation measure, specifically an educational material in the form of prescriber's guide and patient guide, is considered to be necessary for the important identified risks of endophthalmitis (likely infectious origin), intraocular inflammation, transient intraocular pressure increase, retinal pigment epithelium tears, and cataract (especially of traumatic origin), as well as for the important potential risk of medication errors, off-label use and misuse, embryo-fetotoxicity. Generally, the educational material covers the indications wet AMD, branch or central retinal vein occlusion (RVO), diabetic macular (DME) and myopic choroidal neovascularisation (myopic CNV).

The educational material for HCPs 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. In addition, the patient guide is also available in an audio version.

Objectives and 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 in adult population. The following risks are addressed in the educational material: endophthalmitis/intraocular inflammation, transient intraocular pressure increase, RPE tear, cataract, medication error, off label use and misuse, and embryo-fetotoxicity.

Target audience and planned distribution path

The target audience are healthcare professionals (HCPs) specialized in intravitreal injections of anti-VEGF agents as well as patients to be treated. The key messages of the educational materials (provided in Part VII Annex 6) will be distributed electronically 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 EU member states, as requested per GVP Module XVI addendum.

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

Through Routine PV activity.

V.3. Summary of risk minimisation measures

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

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Endophthalmitis (likely infectious origin)	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4 and 4.8. PIL sections 2, 3 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational material: - Prescriber's guide (with an intravitreal injection procedure video and pictogram if nationally required) - Patient guide and its audio version	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific follow-up questionnaire will be used for any reports suspicious for endophthalmitis and intraocular inflammation. Additional pharmacovigilance activities: None.
Intraocular inflammation	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4 and 4.8. PIL sections 2, 3 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational material: - Prescriber's guide (with an intravitreal injection procedure video and pictogram if nationally required) - Patient guide and its audio version	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific follow-up questionnaire will be used for any reports suspicious for endophthalmitis and intraocular inflammation. Additional pharmacovigilance activities: None.

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Transient intraocular pressure increase	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 and 4.9. PIL sections 2 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational material: - Prescriber's guide (with an intravitreal injection procedure video and pictogram if nationally required) - Patient guide and its audio version	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific follow-up questionnaire will be used for report regarding IOP increase following the use of the Afiveg pre-filled syringe. Additional pharmacovigilance activities: None.
Retinal pigment epithelial tears	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PIL sections 2 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational material: - Prescriber's guide (with an intravitreal injection procedure video and pictogram if nationally required) - Patient guide 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 minimisation measures: SmPC sections 4.2, 4.4 and 4.8. PIL sections 2, 3 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational material: - Prescriber's guide (with an intravitreal injection procedure video and pictogram if nationally required) - Patient guide and its audio version	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Medication errors	Routine risk minimisation measures: SmPC sections 4.2, 4.9 and 6.6. PIL sections 1 and 3. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational material: - Prescriber's guide (with an intravitreal injection procedure video and pictogram if nationally required) - Patient guide 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 minimisation measures: SmPC sections 4.1, 4.3, 4.4 and 4.6 PIL sections 1, 2 and 3. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational material: - Prescriber's guide (with an intravitreal injection procedure video and pictogram if nationally required) - Patient guide and its audio version	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Embryo-fetotoxicity	Routine risk minimisation measures: SmPC sections 4.4, 4.6 and 5.3. PIL section 2. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational material: - Prescriber's guide (with an intravitreal injection procedure video and pictogram if nationally required) - Patient guide and its audio version	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Part VI: Summary of the risk management plan

Summary of risk management plan for Afiveg 40 mg/mL solution for injection in pre-filled syringe & Afiveg 40 mg/mL solution for injection (Aflibercept)

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

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

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

I. The medicine and what it is used for

Afiveg 40 mg/mL solution for injection in pre-filled syringe and Afiveg 40 mg/mL solution for injection (in a vial) is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to diabetic macular oedema (DME) 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 Afiveg's benefits can be found in Afiveg's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: (link to the EPAR summary landing page).

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

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

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

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

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

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

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

II.A List of important risks and missing information

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

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

II.B Summary of important risks

Important identified risk: Endophthalmitis (likely infectious origin)	
Evidence for linking the risk to the medicine	Endophthalmitis cases have been observed in the clinical trial program of the originator. Endophthalmitis cases (and other cases of intraocular inflammation) have been reported in post-marketing setting of the originator. The proportion of adult patients exposed to aflibercept who experienced endophthalmitis in the study eye in the clinical studies with the originator was low (range from 0% to 0.9%). Endophthalmitis is regarded as an uncommon ADR. Endophthalmitis cases (and other cases of intraocular inflammation) reported in post-marketing setting are subject to additional follow-up using specific questionnaires.
Risk factors and risk groups	Improper aseptic technique increases the risk of intraocular inflammation.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4 and 4.8. Patient Information Leaflet (PIL) sections 2, 3 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational material: - Prescriber's guide (with an intravitreal injection procedure video and pictogram if nationally required) - Patient guide and its audio version

Important identified risk: Intraocular inflammation	
Evidence for linking the risk to the medicine	Intraocular inflammation cases have been observed in the clinical trial program of the originator. Endophthalmitis and other cases of intraocular inflammation have been reported in post-marketing setting of the originator. The proportion of adult patients exposed to aflibercept who experienced intraocular inflammation in the study eye in the clinical studies with the originator ranged from 0% to 2.6%. Single preferred terms events associated with intraocular inflammation are considered uncommon ADRs (e.g., iritis, uveitis, iridocyclitis) or rare ADRs (vitritis, hypopyon). Endophthalmitis and other cases of intraocular inflammation reported in post-marketing setting are subject to additional follow-up using specific questionnaires.
Risk factors and risk groups	Improper aseptic technique increases the risk of intraocular inflammation.

Important identified risk: Intraocular inflammation	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4 and 4.8. PIL sections 2, 3 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational material: - Prescriber's guide (with an intravitreal injection procedure video and pictogram if nationally required) - Patient guide and its audio version

Important identified risk: Transient intraocular pressure increase	
Evidence for linking the risk to the medicine	The proportion of adult patients exposed to aflibercept who experienced an increase in intraocular pressure in the study eye in the clinical studies with the originator ranged from 2.8% to 13.6%, but the vast majority of these events were resolved. Systematic measurements of IOP during the course of the clinical studies with the originator did not indicate a trend towards sustained IOP increase. The single preferred term "Intraocular pressure increased" is considered a common ADR. Transient intraocular pressure increase reported in post- marketing setting are subject to additional follow-up using specific questionnaires.
Risk factors and risk groups	Patients with glaucoma. Increased intraocular pressure is a known adverse drug reaction on treatment with intravitreal corticosteroids.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 and 4.9. PIL sections 2 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational material: - Prescriber's guide (with an intravitreal injection procedure video and pictogram if nationally required) - Patient guide and its audio version

Important identified risk: Retinal pigment epithelial tears	
Evidence for linking the risk to the medicine	RPE tear is considered a common ADR. However, the total incidence of RPE tears in the AMD Phase III clinical trials of the originator was in line with the known background incidences from literature and the absence of RPE tear in the clinical studies investigating the non-AMD indications of the originator suggests that RPE tear development caused by IVT treatment with aflibercept is rather unlikely.
Risk factors and risk groups	Wet AMD with pigment epithelial detachment; treatment of neovascularization.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC sections 4.4 and 4.8. PIL sections 2 and 4. Legal status: Restricted medical prescription. <u>Additional risk minimisation measures:</u> Educational material: - Prescriber's guide (with an intravitreal injection procedure video and pictogram if nationally required) - Patient guide and its audio version

Important identified risk: Cataract (especially of traumatic origin)	
Evidence for linking the risk to the medicine	The proportion of adult patients exposed to aflibercept who experienced traumatic cataract in the study eye in the clinical studies with the originator ranged from 0% to 2.8%. Various forms of cataract (cortical, nuclear, subcapsular) are considered common ADRs; traumatic cataract is regarded as a rare ADR. There is currently no evidence that the occurrence of a traumatic cataract is increased on treatment with aflibercept. However, as this might be a hypothetical result of the lens perforation, it has been included as important identified risk.
Risk factors and risk groups	Cataract is a known adverse drug reaction on treatment with IVT corticosteroids.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC sections 4.2, 4.4 and 4.8. PIL sections 2, 3 and 4. Legal status: Restricted medical prescription.

Important identified risk: Cataract (especially of traumatic origin)	
	Additional risk minimisation measures: Educational material: - Prescriber's guide (with an intravitreal injection procedure video and pictogram if nationally required) - Patient guide and its audio version

Important potential risk: Medication errors	
Evidence for linking the risk to the medicine	Two milligram (2 mg) aflibercept is provided in vial or a pre-filled syringe format. In both vial and PFS presentations, excess volume is to be expelled during the priming step before injecting the recommended dose. Thus, injecting the entire volume of the pre-filled syringe/vial would result in overdose. However, this numerical overdose is limited, and the drug will be administered only by qualified physicians (not by patients), and this reduces the risk of inappropriate dosing and administration as well. Proper adherence to the instructions for use when using the PFS/vial is key to avoid overdosing.
Risk factors and risk groups	Not applicable.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.9. and 6.6 PIL sections 1 and 3. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational material: - Prescriber's guide (with an intravitreal injection procedure video and pictogram if nationally required) - Patient guide and its audio version

Important potential risk: Off-label use and misuse	
Evidence for linking the risk to the medicine	As with other drugs, Afiveg might be intentionally used other than recommended, or in clinical conditions outside the approved indications (off-label use). Since the clinical experience with Afiveg in such off-label use will be limited (in particular in terms of efficacy and safety), any case of off-label use will be considered a potential risk. Since Afiveg has no dependence potential, the risk of misuse is regarded as very low.
Risk factors and risk groups	Not applicable.

Important potential risk: Off-label use and misuse	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.1, 4.3, 4.4 and 4.6. PIL sections 1, 2 and 3. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational material: - Prescriber's guide (with an intravitreal injection procedure video and pictogram if nationally required) - Patient guide and its audio version

Important potential risk: Embryo-fetotoxicity	
Evidence for linking the risk to the medicine	Testing of the originator product in animals was performed as a standard part of the development of the originator product. It was noted that originator product given in extremely high doses to animals (by far exceeding the doses which would be given to humans) might have an adverse influence on prenatal development (i.e., during the embryonic or foetal development period; so-called embryo-fetotoxicity). Therefore, embryo-fetotoxicity is regarded as a potential risk of treatment with originator product. However, originator product injected locally and at a dose that is distinctively lower than the exposure in animals under which the critical events were observed. So far, there is no relevant indication that treatment with originator product might be associated with embryo-fetotoxicity.
Risk factors and risk groups	Patients at risk are women of childbearing potential.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.6 and 5.3. PIL section 2. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational material: - Prescriber's guide (with an intravitreal injection procedure video and pictogram if nationally required) - Patient guide and its audio version

II.C Post-authorisation development plan

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

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

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

There are no studies required for Afiveg.

Part VII: Annexes

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Annex 4.1: Questionnaire - Endophthalmitis and intraocular inflammation (IOI)

SECTION I- REFERENCE ID		
Company 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 onset of event)	**Gender:** ☐ **male** ☐ **female**	**Weight: unit: Kg/lbs** / **Height: unit: Kg/lbs**
SECTION III· PRODUCT INFORMATION Afiveg		
Therapy date: (dd/mm/yyyy): ☐ **ongoing**		
Indication:	**Number of Afiveg doses before the event:**	
Eye injected: ☐**OS** ☐**OD** ☐ **OU**		
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_____**		

Vial	**PFS (Pre-filled syringe)**
Lot/Batch number:	Lot/Batch number:
Was the same vial used for more than one patient? ☐ Yes ☐ No If yes, did an event occur in other patients? ☐ Yes ☐ No If yes, how many? _____	Was the same PFS used for more than one patient? ☐ Yes ☐ No If yes, did an event occur in other patients? ☐ Yes ☐ No If yes, how many? _____
Was the vial aliquoted in several syringes? ☐ Yes ☐ No Was the vial multipunctured? ☐ Yes ☐ No	
Was the supplied filter needle used? ☐ Yes ☐ No ☐ Unknown	
Date and time of injection preparation:	Date and time of injection preparation:
What was used for injection? ☐ Injection needle Batch No:_____ ☐ Syringe (Luer lock: ☐ yes ☐ no) ☐ Glass ☐ Plastic Batch No: _____	☐ Injection needle Batch No:_____
Where was the syringe for injection prepared? ☐ Off-site pharmacy ☐ On-site pharmacy ☐ Treatment / Examining room	

Vial	PFS (Pre-filled syringe)
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/hh: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/ is resolving, did the visual acuity (VA) recover to:
☐ same level before AE started
☐ VA is worse

Clinical presentation:

Treatment of adverse event

Treatment provided: ☐ **Yes** ☐ **No** **If yes specify:**	☐ **Antibiotics:**	☐ **Steroids** (regimen details):	☐ **Surgery (vitrectomy):** **Date:**	☐ **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 Afiveg**
☐ **Related to intravitreal injection procedure**
☐ **Not related to Afiveg or 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 ☐ UNK**	**Did the event reoccur upon resuming treatment:** ☐ **YES ☐ NO ☐ UNK**

SECTION IV – Relevant Clinical Symptoms (to AE of interest) **Please indicate which eye affected**

Symptom	**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 injections**	**Indication**	**Similar event occurred? If yes, please specify**
☐ **Anti VEGF** Please specify: _____ ☐ **OS** ☐ **OD** ☐ **OU**			☐			
☐ **Other** Please specify: _____ ☐ **OS** ☐ **OD** ☐ **OU**			☐			

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

Condition	**Start Date** *(dd/mm/yyyy)*	**Stop Date** *(dd/mm/yyyy)*	**Ongoing?**
☐ **Diabetes**			☐
☐ **Autoimmune disease, please specify: _____**			☐
☐ **Immunodeficiency, please specify:** _____			☐
☐ **Other, please specify: _____**			☐

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

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

Please sign electronically:

If your signature is not yet configured on your computer, please follow the instruction when you click in the signature field

Signature:

Annex 4.2: Questionnaire - Intraocular pressure (IOP) with pre-filled syringes (PFS) of Afiveg

Reporter information	**Name:** **Email:**								☐ **Physician** ☐ **Nurse** ☐ **Other:**							
Institution Name and address									Telephone: Fax:							
Patient Information	**Initials** *(leave empty for study participants)*		☐ **Male** ☐ **Female**						**Age** (at onset of event)							
Product information	Number of Afiveg doses before event:		**Date of expiry:** DD/MM/YYYY						**PFS batch number(s):**							
Indication:									Eye injected: ☐ OS ☐ OD ☐ OU							
Adverse Event (AE) Information	Intraocular Pressure (IOP) Increase onset date								Last Injection date before event onset:							
	D	D	M	M	Y	Y	Y	Y	D	D	M	M	Y	Y	Y	Y
Was the IOP value measured pre-injection? ☐ NO ☐ Yes, if yes, please provide • IOP value(s) (mmHg) • Time/minutes pre-injection and date • Method																
Was the IOP value measured post-injection? ☐ No ☐ Yes, if yes, please provide • IOP value(s) (mmHg) • Timing(s)/minutes post-injection and dates • 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 detail sequelae: ☐ 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 box to the right.**									**Outcome of events** (please indicate event in parenthesis): ☐ recovering/resolving (event(s)): ☐ recovered/resolved (event(s)): ☐ recovered/resolved with sequelae, (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																

Was there any intervention done to treat increased IOP? ☐ No ☐ Yes, if yes, please specify the 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 detail result, 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 potentially increase IOP? ☐ No ☐ Yes, if yes, please specify the drug names and indications	

Does the patient have any of the following co-morbid 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 ☐ corneal arcus present, details:

PFS details

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

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

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

Were all the 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 dosing line)? ☐ Yes ☐ No,
If No, please provide details:

Was there any difficulty in preparing I the PFS according to the instructions prior to the injection? ☐ No ☐ Yes, if yes, please 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 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	Afiveg: ☐ Vial ☐ PFS Other Intravitreal injections ☐	Was IOP increase also observed after previous intraocular injections? ☐ No ☐ Yes, please detail:

Further notes (*free text*):

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

Draft key messages of the additional risk minimisation measures

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

- Prescriber's Guide (for adult population only)
- Intravitreal injection procedure video for prescribers (if nationally required)
- Intravitreal injection procedure pictogram (if nationally required)
- Patient Guide (for adult population only)

The **Prescriber's Guide** contains the following key elements:

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

The patient information pack of the educational material for the adult population includes a patient information guide and an online link to its audio version. The **Patient Guide** shall be provided to the patient by the treating physician and contains the following key elements:

- Patient information leaflet
- Who should be treated with Afiveg
- How to prepare for Afiveg treatment
- What are the steps following treatment with Afiveg
- 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 healthcare professional
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Afiveg