EU Risk Management Plan for Vgenfli (aflibercept) 40 mg/mL solution for injection in pre-filled syringe, Vgenfli (aflibercept) 40 mg/mL solution for injection in a vial

RMP code: PVRMP-584-01-EU-BIO-CEN

RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data lock point for this RMP: 09-Sep-2024

Date of final sign-off: 23-Jun-2025

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

Summary of significant changes in this RMP: Not applicable – first version of this RMP

QPPV name: Anna Kończak

The content of this RMP has been reviewed and endorsed by QPPV.

Table of content

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Aflibercept
Pharmacotherapeutic group(s) (ATC Code)	Ophtalmologicals, Ocular vascular disorder agents, Antineovascularisation agents (S01LA05)
Marketing Authorisation Applicant	Pharmaceutical Works Polpharma S.A.
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	Vgenfli 40 mg/mL solution for injection in pre-filled syringe, Vgenfli 40 mg/mL solution for injection in a vial
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class Aflibercept is a recombinant fusion protein consisting of portions of human VEGF (Vascular Endothelial Growth Factor) receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1. Aflibercept is a specific blocker that binds and inactivates vascular endothelial growth factor (VEGF) and the related molecule, placental growth factor (PlGF).
	Summary of mode of action Aflibercept 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 (e.g. origin of active substance for biologicals, relevant adjuvants or residues for vaccines) Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.
Hyperlink to the Product Information	Please refer to the module 1.3.1 of eCTD sequence No 0000

Indication(s) in the EEA	Current: *Adults* Vgenfli 40 mg/mL (2 mg dose) is indicated for adults for the treatment of: • Neovascular (wet) age-related macular degeneration (AMD). • Visual impairment due to macular 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: In *adult* patients, the injection volume of Vgenfli is 50 microlitres (µL) (equivalent to 2 mg aflibercept). <u>Wet AMD</u> The recommended dose for Vgenfli 40 mg/mL is 2 mg aflibercept, equivalent to 50 microlitres. <u>Macular oedema secondary to RVO</u> The recommended dose for Vgenfli 40 mg/mL is 2 mg aflibercept, equivalent to 50 microlitres. <u>Diabetic macular oedema</u> The recommended dose for Vgenfli 40 mg/mL is 2 mg aflibercept, equivalent to 50 microlitres. <u>Myopic CNV</u> The recommended dose for Vgenfli 40 mg/mL is 2 mg aflibercept, equivalent to 50 microlitres.
	Proposed (if applicable): Not applicable.
	Current (if applicable):

Pharmaceutical form(s) and strengths	40 mg/mL solution for injection in Type I glass vials and cyclo-olefin polymer (COP) pre-filled syringes (PFS).
	Proposed (if applicable):
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

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

This Module has not been populated because not applicable to an application according to Article 10(4) of Directive 2001/83/EC, as amended (biosimilar medicinal product).

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

The nonclinical development programme of Vgenfli was designed to compare similarity with the reference biologic medicinal product (Eylea; Bayer AG) in bio-functional attributes with highest relevance to product safety and potency.

For structural characterization, key product quality attributes assessed included primary and higher-order protein structure, glycan structure, product-related substances, purity, content, and general properties.

Functional similarity assessments for Vgenfli and EU-Eylea compared target and receptor binding and *in vitro* cell-based potency. The attributes assessed included inhibition of VEGF induced cell proliferation assay, target binding for VEGF-A165, binding to isoforms and other related receptors, selectivity for VEGF family members, neutralization of the VEGF signalling pathway and confirming lack of effector functions based on absence of ADCC- as well as CDC-activity.

Therefore, no safety specifications emerged from the nonclinical development programme by the applicant.

Key safety findings from non-clinical studies and relevance to human usage were considered according the available data on the toxicology and safety pharmacology program conducted by the originator on aflibercept and any relevant published data.

None of the non-clinical findings examined are considered a safety concern for aflibercept requiring risk management activities other than information *via* the suggested product information.

Toxicity

- key issues identified from acute or repeat-dose toxicity studies: Effects in non-clinical studies on repeated dose toxicity were observed only at systemic exposures considered substantially in excess of the maximum human exposure after intravitreal administration at the intended clinical dose indicating little relevance to clinical use.
- reproductive/developmental toxicity: A developmental NOAEL was not identified. At the 0.1 mg/kg dose, the systemic exposures based on C_{max} and cumulative AUC for free aflibercept were approximately 17- and 10-fold higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg.
- genotoxicity, carcinogenicity: No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept.

Safety pharmacology

Not applicable.

Other toxicity-related information or data

Not applicable.

Part II: Module SIII - Clinical trial exposure

Vgenfli is a proposed biosimilar of Eylea® having aflibercept as the active substance. The applicant carried out a phase III randomized, double-masked, parallel-group, multicentre study to compare the efficacy, safety, tolerability, pharmacokinetics, and immunogenicity between Vgenfli and Eylea® in subjects with neovascular age-related macular degeneration (AMD) (Study Vgenfli-CP101).

This study was conducted at 132 study sites in the following 14 countries: Australia (4 study sites); Bulgaria (3 study sites); Czech Republic (2 study sites); Hungary (7 study sites); India (7 study sites); Israel (13 study sites); Japan (22 study sites); Republic of Korea (26 study sites); Latvia (4 study sites); Poland (15 study sites); Russian Federation (4 study sites); Slovakia (4 study sites); Spain (9 study sites); and USA (12 study sites).

Approximately 560 subjects with wet AMD were planned to be enrolled in this study across approximately 155 sites in 14 countries. The study consisted of a screening period of up to 3 weeks, a treatment period of up to 48 weeks, and a post-treatment follow-up period of up to 4 weeks. The total duration of study participation was up to 55 weeks. A total of 914 subjects were assessed for eligibility across 132 sites in 14 countries. A total of 576 subjects were randomly assigned to receive either Vgenfli (288 subjects) or Eylea (288 subjects) treatment.

The study randomized 60 Japanese subjects (30 subjects randomized to each of Vgenfli and Eylea groups) and 516 non-Japanese subjects (258 subjects randomized to each of Vgenfli and Eylea groups).

Table SIII.1: Duration of exposure

Cumulative for all indications (person time)		
Duration of exposure	Patients	Person time
≥6 m	259	87024 days
Total person time	87024 days	

Age group and gender (full analysis set = 287 patients treated with Vgenfli)

A total of 515 subjects (89.4%) had completed the study treatment: 259 subjects (89.9%) in the Vgenfli group and 256 subjects (88.9%) in the Eylea group. A total of 53 Japanese subjects (88.3%) completed the study treatment. All 60 Japanese subjects (100%) completed Week 8 of the study while 56 Japanese subjects (93.3%) had completed the study. A total of 462 non-Japanese subjects (89.5%) completed the study treatment; 506 non-Japanese subjects (98.1%) completed Week 8 of the study while 466 non-Japanese subjects (90.3%) had completed the study.

The mean (SD) age of the subjects was 73.5 (8.27) years. Most subjects were ≥65 years of age. There were 277 males (48.3%) and 296 females (51.7%) in the study; all females were of non-childbearing potential.

The mean (SD) weight of the subjects was 72.32 (14.757) kg and body mass index (BMI) was 26.67 (4.424) kg/m^2.

Ethnic origin

Majority of subjects were of White (382 subjects [66.7%]) or Asian (187 subjects [32.6%]) race and not Hispanic or Latino (554 subjects [96.7%]) ethnicity.

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

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

Pregnancy

Reason for exclusion: Standard ethical criterion for clinical trials.

Is it considered to be included as missing information? No

Rationale: Embryo/foeto-toxicity is included as an important potential risk. This issue is covered in SmPC per the following paragraphs: "Although the systemic exposure after ocular administration is very low, Vgenfli 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." "Embryo-fetotoxicity" is included in this RMP as important potential risk.

"There are no data on the use of aflibercept in pregnant women. Studies in animals have shown embryo-foetal toxicity." No rationale from available data and information that treatment should be considered as missing information under these conditions.

Intraocular pressure (IOP) ≥25 mmHg (in spite of anti-glaucoma treatment)

Reason for exclusion: Aflibercept is known to cause a transient intraocular pressure.

Is it considered to be included as missing information? No

Rationale: Transient intraocular pressure is included as an important identified risk. According to SmPC: "Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with Vgenfli. Special precaution is needed in patients with poorly controlled glaucoma (do not inject Vgenfli 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. No rationale from available data and information that treatment should be considered as missing information under these conditions.

Metabolic dysfunction, uncontrolled hypertension, uncontrolled diabetes mellitus (DME studies: defined as HbA1c >12%), cerebrovascular disease, myocardial infarction, renal failure

Reason for exclusion: Severe systemic disease (including severe systemic infection) was excluded in all trials for technical reasons in order to reduce the impact of potentially confounding factors for safety measurements.

Is it considered to be included as missing information? No

Rationale: No rationale from available data and information that treatment should be considered as missing information under these conditions. Not considered as relevant for the safety profile. According to SmPC: "There is only limited experience in the treatment of subjects with DME due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy. Vgenfli has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment

with Vgenfli in diabetic patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients."

History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use an investigational drug, might affect interpretation of the results of the study, or renders the subject at high risk for treatment complications

Reason for exclusion: Severe systemic disease (including severe systemic infection) was excluded in all trials for technical reasons in order to reduce the impact of potentially confounding factors for safety measurements.

Is it considered to be included as missing information? No

Rationale: No rationale from available data and information that treatment should be considered as missing information under these conditions. Not considered as relevant for the safety profile. According to SmPC: "There is only limited experience in the treatment of subjects with DME due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy. Vgenfli has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with Vgenfli in diabetic patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients."

Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition. There are limited data on safety in the treatment of patients with CRVO, BRVO, DME or myopic CNV with a history of stroke or transient ischaemic attacks or myocardial infarction within the last 6 months. Caution should be exercised when treating such patients."

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.

Furthermore, there now is a 10-year post-marketing experience with 2 mg originator medicinal product and no new rare adverse drug reactions have been identified.

It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than a 100-fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF (2.91 µg/mL) in healthy volunteers. Adverse events due to cumulative effects are not anticipated.

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 program. Pregnancy and lactation constituted exclusion criteria in all clinical trials. There are no adequate and well-controlled studies in pregnant women.
Breastfeeding women	
Paediatric population	There is no relevant use of aflibercept in the paediatric population for the indications of wet AMD, CRVO, BRVO, DME and myopic CNV.
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 program.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

The proposed product is currently non on the market, pending approval of this procedure. In addition, the applicant has no post-authorisation experience in other regions outside EU where the product is already authorised or from other authorised medicinal products containing the same active substance.

Therefore, this section is left empty and will be updated only when the cumulative post-marketing exposure changes to a degree where the considerations on the risk evaluation need also to be updated.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

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

Potential for misuse for illegal purposes

Aflibercept, a recombinant humanized fusion protein, is a vascular endothelial growth factor A (VEGF-A) and placental growth factor (PlGF) antagonist. Aflibercept acts as a soluble decoy receptor that binds to VEGF-A and PlGF and inhibits their biologic activity. VEGF-A and PlGF are angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. Therefore, aflibercept has no central actions, which may trigger the potential for misuse for illegal purposes, e.g. as a recreational drug or to facilitate assault.

Part II: Module SVII - Identified and potential risks

The reference medicinal product (Eylea; Bayer AG) has a published RMP on the website. Therefore, the safety concerns are based on it. Given that the applicant does not register the product for use in the pediatric population, missing information "long-term safety of aflibercept in preterm infants with ROP" is not included in the list of safety concerns.

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

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

The following adverse drug reactions are included in the current SmPC from the originator (version 09/01/2024, MedDRA preferred term level):

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

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

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

Rare: Blindness, cataract traumatic, vitritis, hypopyon.

The conditions, which are regarded as important identified or potential risks (either as single preferred term event term or by term grouping) are underlined in the preceding listing. The remaining risks are not regarded as important for the following reasons 1 to 3:

- **Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):**
    - Visual acuity reduced (very common), vision blurred (common).

Comment: This functional loss is mainly considered to occur because of the underlying ocular disease. It may represent a symptom of an injection related event such as intraocular inflammation/infection or retinal tear/detachment. These complications pose important identified risk in the EU RMP.

- Conjunctival haemorrhage (very common), conjunctival hyperaemia (common), ocular hyperaemia (common), vitreous haemorrhage (common), vitreous floaters (common), eye pain (very common), injection site pain (common), injection site haemorrhage (common), injection site irritation (uncommon), lacrimation increased (common), foreign body sensation in eyes (common), abnormal sensation in eye (uncommon), eyelid irritation (uncommon).

Comment: These are local events likely caused by the intraocular injection procedure, which are usually mild and fully reversible in nature. It is expected that Health Care Professionals (HCPs) are well familiar with these concomitant adverse effects of the IVT injection.

- **Known risks that do not impact the risk-benefit profile (in relation to the severity of the indication treated):**
    - Detachment of retinal pigment epithelium (common), retinal degeneration (common), vitreous detachment (common), corneal erosion (common), corneal abrasion (common), punctate keratitis (common), corneal epithelium defect (uncommon).

Comment: These events are likely procedure-related (however, "detachment of retinal pigment epithelium" and "retinal degeneration" could also be promoted by underlying disease) and may result in longer-term complaints. However, no severe sequelae are expected, and these events are not assumed to impair the positive risk/benefit profile of the product. It is expected that HCPs are well familiar with these potential adverse effects of the IVT injection.

- **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:**
    - Blindness (rare).

Comment: This event is rare and may also occur because of the underlying disease.

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

Potential risk: Sustained intraocular pressure.

Issue: A persistent ocular hypertension (OHT) has been observed after intravitreal injection of VEGF inhibitors (ranibizumab, bevacizumab), leading to an assumed class effect of "sustained" IOP increase. The incidence of sustained OHT after intraocular administration of these VEGF inhibitors ranged between 3.1% and 11.9% (**Agard E, 2015**). Two hypotheses have been described for the underlying mechanism of chronic OHT:

1) The anti-VEGF antibodies (= high molecular proteins) may accumulate in the aqueous outflow channels including the trabecular meshwork or Schlemm´s canal and obstruct aqueous outflow (**Chehab Hel, 2013**).
2) Immunological reactions and low-grade inflammation post-injection may be an additional mechanism leading to IOP elevations (**Sniegowski M, 2010**).

Both effects may be amplified by the quality of the injected VEGF inhibitor: aggregation of the antibody to higher molecular structures may enhance the obstruction of the outflow system. Also, contaminants such as silicone oil from the syringe barrel or rubber stopper may block the outflow system or induce subclinical inflammation (**Bakri SJ, 2008**).

Comment: A transient increase of IOP, which is often observed after intravitreal injection of fluids, is considered an important identified risk of IVT aflibercept administration. It is attributed to an increase in vitreous volume (volume effect), which is compensated within 0.5 to 1 hours after injection, so that IOP normalizes back to baseline values (Agard E, 2015). Therefore, the volume effect is not responsible for a chronic elevation of IOP. Therefore, the assumed class effect of "sustained" IOP increase is not regarded as an important risk of treatment with aflibercept.

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

An overview of the important identified and potential risks of aflibercept is provided in the next paragraphs.

Important Identified Risk 1: Endophthalmitis (likely infectious origin)

Risk-benefit impact: Endophthalmitis is an intraocular infection and 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). 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).

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

Endophthalmitis cases (and other cases of intraocular inflammation) that will be reported in post-marketing setting will be subject to additional follow-up using specific questionnaires. Currently, the risk-benefit in terms of endophthalmitis is considered favourable for aflibercept.

Important Identified Risk 2: Intraocular inflammation

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

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

Single preferred terms events associated with intraocular inflammation are considered uncommon ADRs (e.g., iritis, uveitis, iridocyclitis) or rate ADRs (vitritis, hypopyon). Endophthalmitis and other cases of intraocular inflammation that will be reported in post-marketing setting will be subject to additional follow-up using specific questionnaires. Currently, the risk-benefit in terms of intraocular inflammation is considered favourable for aflibercept.

Important Identified Risk 3: Transient intraocular pressure increase

Risk-benefit impact: Chronically elevated intraocular 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., normal-tension glaucoma).

Transient IOP increase following IVT injection is a well- known side effect of any IVT administration of liquids used for drug dissolution, but this condition is limited and usually resolved once the surplus fluid has been resorbed from the inner eye.

"Intraocular pressure increased" (single preferred term) is considered a common ADR. Transient intraocular pressure increase that will be reported in post-marketing setting will be subject to additional follow-up using specific questionnaires. Currently, the risk-benefit in terms of transient IOP increase is considered favourable for aflibercept.

Important Identified Risk 4: Retinal pigment epithelial (RPE) tears

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

Published data suggest that RPE tear development caused by IVT treatment with aflibercept is rather unlikely (**Saito M, 2013**). Data from VigiAccess show that retinal pigment epithelial tears were recorded in only 148 eyes, out of 28524 reports from 2008 until 14 January 2024. Currently, the risk-benefit in terms of RPE tear is considered favourable for aflibercept.

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

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

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

Various forms of cataract (cortical, nuclear, subcapsular) are considered common ADRs; traumatic cataract is regarded as a rare ADR.

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

included as important identified risk. Currently, the risk-benefit in terms of cataract (especially of traumatic origin) is considered favourable for aflibercept.

The following section summarizes the identified potential risks of aflibercept. This group mainly includes the class effects known from systematically administered VEGF inhibitors as well as off-label use and medication error.

Important Potential Risk 1: Medication error

Risk-benefit impact: There is an excess volume in the proposed vial which exceeds the recommended net dose of 2 mg Vgenfli per injection. Thus, injection of more than the approved volume results in overdose. However, this numerical overdose is limited, and the drug will be administered only by qualified physicians (not by patients), and this reduces the risk of inappropriate dosing and administration as well. No clinically meaningful events of overdose have been reported so far (neither in clinical trials nor in usual care); only 28 ADRs related to overdose have been reported, out of 28524 reports from 2008 until 14 January 2024 (data from VigiAccess). Nevertheless, it was decided to consider "medication error " a potential risk of treatment, which is, however, completely avoidable by proper adherence to the dosing recommendations.

Important Potential Risk 2: Off-label use and misuse

Risk-benefit impact: As with other drugs, Vgenfli might be intentionally used other than recommended, or in clinical conditions outside the approved indications. Vgenfli does not have any dependence potential. Since the applicant does not have clinical experience with Vgenfli in such off- label use, 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) can occur with Vgenfli. The Vgenfli vial is proposed for single eye use only.

Important Potential Risk 3: Embryo-fetotoxicity

Risk-benefit impact: As angiogenesis is a critical component of embryonic and foetal 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 (**Polizzi S, 2015**). However, early loss of pregnancy after IVT bevacizumab injection has been reported in a very few instances (**Sullivan L, 2014**). Therefore, particular attention is paid to that safety issue.

Missing information: None

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

Not applicable.

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

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

SVII.3.1.1 Important Identified Risk: Endophthalmitis (likely infectious origin) (MedDRA codes: 10014801; 10073350)

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:

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). The proportion of aflibercept-exposed adult patients who experienced endophthalmitis in the study eye in the clinical studies with aflibercept ranged from 0% to 0.9% (**Carrasco J, 2021**). Endophthalmitis was reported in 1 subject [0.3%] each in the Vgenfli group (Study Vgenfli-CP101).

Characterisation of the risk:

Infectious endophthalmitis remains one of the most devastating complications of intravitreal injections. In multicentre clinical trials with anti-VEGF therapy the incidence of endophthalmitis per patient has been reported to range from 0.019 to 1.6%. However, the reported rate in the recent studies tends to be lower than that in early trials. The rate of endophthalmitis seems to be the same among different anti-VEGF agents, different injection settings, and different geographical locations. Recent studies reported that endophthalmitis caused by *Streptococcus* species was significantly more frequent after intravitreal injection than after intraocular surgery. Considering the fact that *Streptococcus* species comprise at least 41% culturable adult salivary flora, the difference in causative organisms in these two settings has been attributed to the contamination of injection field by aerosolization or droplet spread (**Falavarjani KG, 2013**).

Recently, a retrospective case series described the incidence of endophthalmitis and the treatment outcomes of acute bacterial endophthalmitis following intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections in a Brazilian hospital. The analysis was based on the timing of infection after intravitreal injection, culture results, visual acuity, and the presence of epiretinal membrane after a 1-year follow-up period, spanning nine years. This retrospective case series, conducted over a 9-year period, aimed to evaluate the treatment outcomes of acute endophthalmitis following intravitreal Bevacizumab injections. The inclusion criteria involved a chart review of 25 patients who presented clinical signs of acute endophthalmitis out of a total of 12,441 injections administered between January 2011 and December 2019. Negative culture results of vitreous samples or incomplete data were excluded. Ultimately, 23 patients were enrolled in the study. Eight patients were treated with intravitreal antibiotic injections (IVAI) using vancomycin 1.0 mg/0.05mL and ceftazidime 2.25 mg/0.05mL, while 15 patients underwent pars plana vitrectomy (PPV) followed by intravitreal antibiotic injections at the end of surgery (IVAIES). The main outcome measures were the efficacy of controlling the infection with IVAI as a standalone therapy compared to early PPV followed by IVAIES. Data collected included pre-infection and one-year post-treatment best corrected visual acuity (BCVA), optical coherence tomography (OCT) abnormalities, and enucleation/evisceration rates. To compare groups, Mann-Whitney and ANOVA tests were employed for statistical analysis. The incidence rate of bacterial endophthalmitis was 0.185% (1/541 anti-VEGF injections), with the highest infection rates observed in 2014 and 2017. Patients presented clinical symptoms between 2 and 7 days after injection. The most common isolated organisms were coagulase-negative Staphylococci and Streptococci spp. Treatment outcomes showed that both IVAI and PPV + IVAIES effectively controlled the infection and prevented globe atrophy. After one year, the PPV group with BCVA better than Light Perception had a significantly better BCVA compared to the IVAI group (p = 0.003). However, PPV group had higher incidence of epiretinal membranes formation compared to the IVAI group. (p = 0.035). It was concluded that anti-VEGF injections carry a risk of developing acute bacterial endophthalmitis. Isolated antibiotic therapy could be an effective treatment to control the infection, but performing PPV + IVAIES as a primary treatment showed promising results in terms of improving BCVA after one year, despite a higher rate of epiretinal membrane formation (**Bergamo VC, 2023**).

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

Risk factors and risk groups:

Improper aseptic technique increases the risk of intraocular inflammation.

Preventability:

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:

An educational program will be performed as an additional risk minimization measure to raise patients´ and physicians´ awareness on identified and potential risks. Furthermore, a specific questionnaire will be used to gain more knowledge about this risk.

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

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.

SVII.3.1.2 Important Identified Risk: Intraocular inflammation (MedDRA code: 10082041)

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 aetiology 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.

The main factors which play a role in intraocular inflammation after anti-VEGF injection can be divided into three causes: patient-specific, medication-specific and delivery-specific. The majority of clinically significant inflammation seen after intravitreal injection is an acute onset inflammatory response with most patients recovering baseline VA in 3–5 weeks. The presence of pain, hypopyon, severe anterior chamber reaction, hyperaemia and significant vision loss may help distinguish infectious from non-infectious aetiologies of post injection inflammation. Avoiding temperature fluctuation, mechanical shock, agitation during transport and handling of syringes/drugs, and the use of SO-free syringes may help minimize intraocular inflammation. While a definitive mechanism has not yet been established, current knowledge of the clinical presentation and vitreous histopathology of brolucizumab-retinal vasculitis favours an auto-immune type IV hypersensitivity reaction (**Anderson VJ, 2021**).

Evidence source(s) and strength of evidence:

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) (**Marticorena J, 2012**).

Characterisation of the risk:

The proportion of aflibercept-exposed adult patients who experienced intraocular inflammation in the study eye in clinical studies was very low, from 0% (**Chen Y-X, 2020**; **Okada AA, 2022**) to 0.4% (**Woo SJ, 2023**).

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

Risk factors and risk groups:

Improper aseptic technique increases the risk of intraocular inflammation.

Preventability:

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) in order to enable the treating physician to introduce appropriate countermeasures in due time.

Impact on the risk-benefit balance of the product:

An educational program will be performed as an additional risk minimization measure to raise patients´ and physicians´ awareness on identified and potential risks. Furthermore, a specific questionnaire will be used to gain more knowledge about this risk.

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

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.

SVII.3.1.3 Important Identified Risk: Transient intraocular pressure increase (MedRA codes: 10022801; 10021667)

Potential mechanisms:

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

Evidence source(s) and strength of evidence:

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.

Characterisation of the risk:

The proportion of aflibercept-exposed adult patients who experienced an increase in intraocular pressure in the study eye in the clinical studies ranged from 2.2% (**Okada AA, 2022**) to 3.1% (**Chen Y-X, 2020**). In the vast majority of patients across all treatment groups, the reported IOP increase was only transient and was resolved.

Risk factors and risk groups:

Patients with glaucoma.

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

Preventability:

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

Impact on the risk-benefit balance of the product:

An educational program will be performed as an additional risk minimization measure to raise patients´ and physicians´ awareness on identified and potential risks. Furthermore, a specific questionnaire will be used to gain more knowledge about this risk.

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

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.

SVII.3.1.4 Important Identified Risk: Retinal pigment epithelial tear (MedRA Code: 10062971)

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 (**Clemens CR, 2016**; **Empeslidis T, 2014**).

Evidence source(s) and strength of evidence:

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

Characterisation of the risk:

The proportion of aflibercept-exposed adult patients who experienced a retinal pigment epithelial tears in the study eye in the clinical studies was very low (**Stahl A, 2022**; **Woo SJ, 2023**). Retinal pigment epithelial tears were reported in 3 subjects [1.0%] in the Vgenfli group (Study Vgenfli-CP101).

RPE tears have also been reported following treatment of the neovascularization, regardless of whether the treatment was delivered intravitreally (pegaptanib sodium, bevacizumab, ranibizumab) or through other means (argon or krypton laser photocoagulation, transpupillary thermotherapy, photodynamic therapy with verteporfin) (**Clemens CR, 2016**).

RPE tears may lead to a loss of vision (and thus to legal blindness).

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:

An educational program will be performed as an additional risk minimization measure to raise patients´ and physicians´ awareness on identified and potential risks.

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

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.

SVII.3.1.5 Important Identified Risk: Cataract (especially of traumatic origin) (MedDRA codes: 10007739; 10044515)

Potential mechanisms:

Related to IVT procedure.

Evidence source(s) and strength of evidence:

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

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

Characterisation of the risk:

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

The proportion of aflibercept -exposed adult patients who experienced traumatic cataract in the study eye in the clinical studies ranged from 0.5% to 1.7% (**Pielen A, 2017**; **Mitchell P, 2018**). Cataract (without statement of origin) was reported in 8.1% of patients with AMD in the ALTAIR study (**Ohji M, 2020**). In the VISTA/VIVID studies, compared to aflibercept, there was a higher incidence of increased intraocular pressure and cataract formation in patients treated with dexamethasone (**Santhakumaran S, 2022**).

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

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:

An educational program will be performed as an additional risk minimization measure to raise patients´ and physicians´ awareness on identified and potential risks.

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

Public health impact:

Patients experiencing (traumatic) cataract may require cataract surgery.

SVII.3.1.6 Important Potential Risk: Medication errors (MedDRA code: 10027091)

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 (PFS) 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, because the proposed product is not marketed.

Risk factors and risk groups:

Not applicable.

Preventability:

Instructions on the correct drug preparation and administration will be given in the SmPCs and the educational program in order to minimize the risk of accidental medication errors.

Impact on the risk-benefit balance of the product:

An educational program will be performed as an additional risk minimization measure to raise patients´ and physicians´ awareness on identified and potential risks.

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

Public health impact:

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

SVII.3.1.7 Important Potential Risk: Off-label use and misuse (MedDRA codes: 10053762; 10065679)

Potential mechanisms:

Not applicable.

Evidence source(s) and strength of evidence:

As with other drugs, Vgenfli might be intentionally used other than recommended, or in clinical conditions outside the approved indications (so-called off-label use). Since the available clinical experience with aflibercept 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 Vgenfli has no dependence potential, the risk of misuse is regarded as very low.

Characterisation of the risk:

Not applicable, because the proposed product is not marketed.

Risk factors and risk groups:

Not applicable.

Preventability:

Most neovascular and VEGF dependent retina diseases including particularly AMD are diseases of the adult. Therefore, the potential for off-label use in the paediatric population is expected to be very limited due to the nature of paediatric ophthalmic diseases. In some rare cases, diabetic retinopathy may occur in adolescents. Some ophthalmologists tend to use off-label anti-VEGF drugs in this disease instead of the approved therapy. Myopic CNV, CRVO, and BRVO may also very rarely occur in adolescents and may be treated off-label with any IVT anti-VEGF drug, including aflibercept. Aflibercept may be also used to treat some cases of retinopathy of prematurity (**Stahl A, 2022**). The number of such cases is considered very low and their care is provided by paediatric ophthalmologists who are tertiary care based and experienced in the care of these infants. Additionally, Vgenfli is not registered for pediatric population and the Applicant placed information in the product information that the product is intended for adults only.

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

Impact on the risk-benefit balance of the product:

An educational program will be performed as an additional risk minimization measure to raise patients´ and physicians´ awareness on identified and potential risks.

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

Public health impact:

Not applicable.

SVII.3.1.8 Important Potential Risk: Embryo-fetotoxicity (MedDRA codes: all under PT pregnancy [10036556])

Potential mechanisms:

VEGF exerts multiple functions, including vasculogenesis and neoangiogenesis and vascular permeability. Animal and human studies have demonstrated a central role of VEGF in the maintenance of foetal and placental vasculature, and a reduced VEGF expression was linked with defective embryogenesis and foetal loss in humans (**Polizzi S, 2015**). Therefore, embryo-fetotoxicity is regarded as a potential risk of treatment with aflibercept.

Evidence source(s) and strength of evidence:

A developmental NOAEL was not identified. At the 0.1 mg/kg dose, the systemic exposures based on C_{max} and cumulative AUC for free aflibercept were approximately 17- and 10-fold higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg (see *Part II, Module SII*).

Characterisation of the risk:

The use of anti-VEGF drugs during pregnancy is controversial because they may potentially cause systemic side effects in the mother and foetal harm, as spontaneous miscarriage, and preeclampsia. The limited clinical experience reported in the literature does not allow to establish a definite correlation between use of anti-VEGF and maternofoetal complications (**Polizzi S, 2015**).

Using the JAPIC AERS database which is composed of the Food and Drug Administration Adverse Event Reporting System (FAERS) dataset pre-processed by the Japan Pharmaceutical Information Center (JAPIC) to investigate the VEGF inhibitors ranibizumab, aflibercept, and bevacizumab, a potential safety signals of pregnancy loss were obtained from intraocular administration of VEGF inhibitors during pregnancy (**Sakai T, 2022**).

Risk factors and risk groups:

Patients at risk are women of childbearing potential.

Preventability:

Treatment with Vgenfli 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:

An educational program will be performed as an additional risk minimization measure to raise patients´ and physicians´ awareness on identified and potential risks.

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

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

SVII.3.2.1 Missing information:

Not applicable. There are no missing information.

Part II: Module SVIII - Summary of the safety concerns

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

Table SVIII.1: Summary of safety concerns

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

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

III.1 Routine pharmacovigilance activities

III.1.1 Specific adverse reaction follow-up questionnaires for safety concerns:

In order to optimize the data collection for defined medical conditions, specific follow-up questionnaires will be used for endophthalmitis/intraocular inflammation, and IOP increases (see **Annex 4**). These specific questionnaires will be used to follow-up on any post-marketing or study reports causing suspicion of these events in order to standardize and increase the completeness of reports.

Table Part III.1: Routine PV activities/questionnaires

Important identified risk		
Routine PV activities beyond adverse reactions reporting and signal detection	**Objectives**	**Important identified risk**
Specific questionnaire to be used for any post-marketing or study reports suspicious for endophthalmitis and intraocular inflammation (see **Annex 4.1**).	Specific questionnaire to obtain comprehensive and standardized follow-up information about cases suspicious for endophthalmitis and intraocular inflammation.	Endophthalmitis (likely infectious origin) and intraocular inflammation.
Specific questionnaire to be used for any post-marketing or study report related to IOP increase following the use of Vgenfli (see **Annex 4.2**).	Specific questionnaire to obtain comprehensive and standardized follow-up information related to intraocular pressure increase following the use of Vgenfli pre-filled syringe.	Transient intraocular pressure increase

III.1.2 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 Vgenfli.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities will be implemented for Vgenfli.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable because no post-authorisation safety study is proposed or imposed for Vgenfli.

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

Risk Minimisation Plan

The following tables provide, per safety concern, an overview of the applied routine and additional risk minimization measures (quoted SmPC text parts are taken from the proposed SmPC).

V.1. Routine Risk Minimisation Measures

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

Safety concern	**Routine risk minimisation activities**
Endophthalmitis (likely infectious origin)	**Routine risk communication**: SmPC section 4.2 (Posology and method of administration) SmPC section 4.3 (Contraindications) SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) Package Leaflet section 2 (What you need to know before you are given Vgenfli) Package Leaflet section 4 (Possible side effects) **Routine risk minimisation activities recommending specific clinical measures to address the risk**: • SmPC Section 4.2 (Posology and method of administration): A comprehensive description of the injection procedure (including short-term follow-up) is provided in order to ensure high-quality standard of the intervention. • SmPC Section 4.2 (Posology and method of administration) and Package Leaflet section 2 (What you need to know before you are given Vgenfli): Suggestive symptoms of endophthalmitis are mentioned. • *"Ocular or periocular infection"* and *"active severe intraocular inflammation"* are listed in SmPC Section 4.3 (Contraindications)

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

	• SmPC Section 4.4 (Special warnings and precautions for use): Potential for immunogenicity with Vgenfli is mentioned (see Section 4.8). Monitoring of symptoms is advised • Package Leaflet section 2 (What you need to know before you are given Vgenfli): Description, monitoring and early treatment of symptoms are mentioned • Package Leaflet section 3 (How you will be given Vgenfli): Description on pre-injection use of disinfectant for cleaning measures provided. **Other routine risk minimisation measures beyond the Product Information**: Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections.

Transient intraocular pressure increase	**Routine risk communication**: SmPC section 4.2 (Posology and method of administration) SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) SmPC section 4.9 (Overdose) Package Leaflet section 2 (What you need to know before you are given Vgenfli) Package Leaflet section 4 (Possible side effects) **Routine risk minimisation activities recommending specific clinical measures to address the risk**: • SmPC Section 4.2 (Posology and method of administration): A comprehensive description of the injection procedure (including short-term follow-up) is provided in order to ensure high-quality standard of the intervention. • SmPC Section 4.2 (Method of administration): Appropriate monitoring for elevation in intraocular pressure is mentioned. Special precaution in patients with poorly controlled glaucoma is mentioned. • SmPC Section 4.4 (Special warnings and precautions for use): Excess volume from the 2 mg Vgenfli pre-filled syringe/vial must be expelled/discarded prior to administration. • Package Leaflet section 2 (What you need to know before you are given Vgenfli): Injections with Vgenfli may cause an increase in eye pressure. • SmPC Section 4.9 (Overdose): Effect of overdosing, monitoring and treatment of intraocular pressure by the physician are mentioned. **Other routine risk minimisation measures beyond the Product Information**: Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections.

Retinal pigment epithelial tears	**Routine risk communication**: SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) Package Leaflet section 2 (What you need to know before you are given Vgenfli) Package Leaflet section 4 (Possible side effects) **Routine risk minimisation activities recommending specific clinical measures to address the risk**: • SmPC Section 4.4 (Special warnings and precautions for use): A description of risk factors is given for retinal pigment epithelial tear (RPE tear) in wet AMD patients and advice to be cautious when initiating Vgenfli therapy in patients with this risk factor. • Package Leaflet section 2 (What you need to know before you are given Vgenfli): Check of risk factors for retinal tear/detachment, RPE tear/detachment by the physician is mentioned. **Other routine risk minimisation measures beyond the Product Information**: Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections.

Cataract (especially of traumatic origin)	**Routine risk communication**: SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) Package Leaflet section 2 (What you need to know before you are given Vgenfli) Package Leaflet section 3 (How you will be given Vgenfli) **Routine risk minimisation activities recommending specific clinical measures to address the risk**: • SmPC Section 4.2 (Posology and method of administration): a comprehensive description of the injection procedure (including short-term follow-up) is provided in order to ensure high-quality standard of the intervention. • SmPC Section 4.4 (Special warnings and precautions for use): Instructions for aseptic injection techniques, monitoring and instructions for patients are mentioned. • Package Leaflet section 2 (What you need to know before you are given Vgenfli): Description, monitoring and early treatment of symptoms are mentioned. • Package Leaflet section 3 (How you will be given Vgenfli): "Before the injection your doctor will use a disinfectant eyewash to clean your eye carefully to prevent infection." **Other routine risk minimisation measures beyond the Product Information**: Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections.

Medication errors	**Routine risk communication**: SmPC section 4.2 (Posology and methods of administration) SmPC section 4.9 (Overdose) SmPC section 6.6 (Special precautions for disposal and other handling) Package Leaflet section 1 (What Vgenfli is and what it is used for) Package Leaflet section 3 (How you will be given Vgenfli) **Routine risk minimisation activities recommending specific clinical measures to address the risk**: • SmPC Section 4.2 (Posology and method of administration) and Package Leaflet section 'information intended for Health Care Professionals (HCPs) only': Verbal instruction is provided for the handling of the pre-filled syringe/vial in order to minimize the risk of drug administration error. • SmPC Section 4.9 (Overdose): Association between overdose and IOP increase is mentioned. • SmPC section 6.6 (Special precautions for disposal and other handling) and Package Leaflet section 'information intended for HCPs only': Instruction for the use of the pre-filled is provided. **Other routine risk minimisation measures beyond the Product Information**: Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections.

Off-label use and misuse	**Routine risk communication**: SmPC section 4.1 (Therapeutic indications) Package Leaflet section 1 (What Vgenfli is and what it is used for) Package Leaflet section 3 (How you will be given Vgenfli) **Routine risk minimisation activities recommending specific clinical measures to address the risk**: • Contraindications are listed in SmPC Section 4.3 (Contraindications) and Package Leaflet section 2 (What you need to know before you are given Vgenfli). • Conditions in which treatment should be withheld/discontinued/not recommended are included in the SmPC section 4.4 and Package Leaflet section 2 (What you need to know before you are given Vgenfli). • Conditions of use in pregnancy and breastfeeding are included in the SmPC section 4.6 and Package Leaflet section 2 (What you need to know before you are given Vgenfli). **Other routine risk minimisation measures beyond the Product Information**: Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections.

Embryo-fetotoxicity	**Routine risk communication**: SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.6 (Fertility, pregnancy and lactation) SmPC section 5.3 (Preclinical safety data) Package Leaflet section 2 (What you need to know before you are given Vgenfli) **Routine risk minimisation activities recommending specific clinical measures to address the risk**: • SmPC Section 4.4 (Special warnings and precautions for use) and Package Leaflet section 2 (What you need to know before you are given Vgenfli): Instructions for pregnancy and women of childbearing potential are mentioned. • SmPC Section 4.6 (Fertility, pregnancy and lactation): Instructions for pregnancy and women of childbearing potential are mentioned. • Package Leaflet section 2 (What you need to know before you are given Vgenfli): Instructions for pregnancy and women of childbearing potential are mentioned. **Other routine risk minimisation measures beyond the Product Information**: Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections.

V.2. Additional Risk Minimisation Measures

V.2.1 Educational Program

Besides routine risk minimization activities (SmPC and patient information), additional activity, specifically an educational program, 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, the preparation and handling of the Vgenfli PFS. Generally, the educational material covers the indications wet AMD, CRVO, BRVO, myopic CNV and DME.

V.2.1.1 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 and to include guidance on the IVT injection procedure using the 2 mg Vgenfli PFS to train physicians in order to minimize injection-related adverse reactions.

Educational material also includes guidance on the IVT injection procedure to re-train physicians in order to minimize injection-related adverse reactions.The following risks are addressed in the Educational Material: endophthalmitis/intraocular inflammation, transient intraocular pressure increase, RPE tear,cataract, medication error, off label use and misuse, and embryo-fetotoxicity.

V.2.1.2 Target audience and planned distribution path

The target audience are 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 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 EU member states, as requested per GVP Module XVI *addendum*.

V.2.1.3 Plans to evaluate the effectiveness of the interventions and criteria for success

The following criteria for judging the success of the proposed risk minimization measures were applied:

- Proportion of physicians who have received the education materials.
- Level of physicians' knowledge and understanding of the updated educational material (i.e., underline information on treatment of women of child-bearing potential, information on the injection procedure with respect to unnecessary dilation of the eye, vision and intraocular pressure evaluation after injection and on potential medication misuse, particularly inadvertent reuse of the vial).

V.3 Summary of risk minimisation measures

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Endophthalmitis (likely infectious origin)	**Routine risk minimisation measures**: SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet section 2, 3 and 4. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, patient guide "Your guide to Vgenfli", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Specific questionnaire to be used for any post-marketing or study reports suspicious for endophthalmitis and intraocular inflammation (see **Annex 4.1**). **Additional pharmacovigilance activities**: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Intraocular inflammation	**Routine risk minimisation measures**: SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet section 2, 3 and 4. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections, **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, patient guide "Your guide to Vgenfli", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Specific questionnaire to be used for any post-marketing or study reports suspicious for endophthalmitis and intraocular inflammation (see **Annex 4.1**). **Additional pharmacovigilance activities**: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Transient intraocular pressure increase	**Routine risk minimisation measures**: SmPC sections 4.2, 4.4, 4.8, and 4.9 Package Leaflet sections 2 and 4. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video; in additionpatient guide "Your guide to Vgenfli", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Specific questionnaire to be used for any post-marketing or study reports suspicious for intraocular pressure increase (see **Annex 4.2**). **Additional pharmacovigilance activities**: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Retinal pigment epithelial tears	**Routine risk minimisation measures**: SmPC sections 4.4 and 4.8 Package Leaflet sections 2 and 4. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video; in additionpatient guide "Your guide to Vgenfli", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Not applicable. **Additional pharmacovigilance activities**: None

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Medication errors	**Routine risk minimisation measures**: SmPC sections 4.2, 4.9 and 6.6 Package Leaflet sections 1 and 3. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on medication error (prescriber guide and video; in additionpatient guide "Your guide to Vgenfli", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Not applicable. **Additional pharmacovigilance activities**: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Off-label use and misuse	**Routine risk minimisation measures**: SmPC sections 4.1, 4.3, 4.4 and 4.6 Package Leaflet sections 1, 2 and 3. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on off-label use (prescriber guide and video; in addition, patient guide "Your guide to Vgenfli", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Not applicable. **Additional pharmacovigilance activities**: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Embryo-fetotoxicity	**Routine risk minimisation measures**: SmPC sections 4.4, 4.6 and 5.3 Package Leaflet section 2. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on the potential risk of embryo-toxicity and to underline information on treatment of women of child-bearing potential, and the need for appropriate contraception in women of childbearing potential (prescriber guide and video; in addition patient guide "Your guide to Vgenfli", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Not applicable. **Additional pharmacovigilance activities**: None

Summary of risk management plan for Vgenfli (Aflibercept) 40 mg/mL solution for injection in pre-filled syringe, Vgenfli (Aflibercept) 40 mg/mL solution for injection in a vial

This is a summary of the EU risk management plan (RMP) for Vgenfli 40 mg/mL (2 mg dose). The RMP details important risks of Vgenfli, how these risks can be minimized, and how more information will be obtained about Vgenfli's risks and uncertainties (missing information).

Vgenfli's 40 mg/mL (0.4/2 mg dose) summary of product characteristics (SmPC) and their package leaflets give essential information to healthcare professionals and patients on how Vgenfli should be used.

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

I. The medicine and what it is used for

Vgenfli 40 mg/mL (2 mg dose) is indicated for adults for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to macular edema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to diabetic macular oedema (DME), and visual impairment due to myopic choroidal neovascularization (myopic CNV; see SmPC for the full indication).

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

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

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

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

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

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

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

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

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

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

If important information that may affect the safe use of Vgenfli is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Vgenfli 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 Vgenfli. 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).

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

II.B Summary of important risks

Important identified risk: Endophthalmitis (likely infectious origin)	
Evidence for linking the risk to the medicine	Data from clinical trials, and literature. The intravitreal injection procedure can implant pathogens into the eye if there is a break in sterile technique. Source of pathogenic agents is in most cases the patient's conjunctival bacterial flora.
Risk factors and risk groups	Improper aseptic technique increases the risk of intraocular inflammation.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet sections 2, 3 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, patient guide "Your guide to Vgenfli", and its audio version).

Important identified risk: Intraocular inflammation	
Evidence for linking the risk to the medicine	Data from clinical trials, and literature. Post-injection, sterile intraocular inflammation is a known risk following intravitreal injections of anti-VEGFs and for other intravitreally applied drugs.
Risk factors and risk groups	Improper aseptic technique increases the risk of intraocular inflammation.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet section 2, 3 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition patient guide "Your guide to Vgenfli", and its audio version).

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

Important identified risk: Retinal pigment epithelial tears	
Evidence for linking the risk to the medicine	Data from clinical trials, and literature. Development of RPE tears after anti-VEGF intravitreal injection has been attributed to a decline in intercellular adherence, thereby increasing susceptibility to tearing of the RPE layer particularly in patients with wet AMD.
Risk factors and risk groups	Wet AMD with pigment epithelial detachment; treatment of neovascularization.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 Package Leaflet sections 2 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimization measures: Educational program for adults: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video, in addition patient guide "Your guide to Vgenfli", and its audio version).

Important identified risk: Cataract (especially of traumatic origin)	
Evidence for linking the risk to the medicine	Data from clinical trials, and literature. Related to IVT procedure.
Risk factors and risk groups	Cataract is a known adverse drug reaction on treatment with IVT corticosteroids.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.4 and 4.8 Package Leaflet sections 2, 3 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition patient guide "Your guide to Vgenfli", and its audio version).

Important potential risk: Medication errors	
Evidence for linking the risk to the medicine	Although 2mg Vgenfli is provided in a pre-filled syringe, there is an excess volume which exceeds the recommended net dose of 2 mg Vgenfli per injection. The drug will be administered only by qualified physicians (not by patients), and this reduces the risk of inappropriate dosing and administration as well. Proper adherence to the instructions for adequate PFS preparation and use minimizes medication errors.
Risk factors and risk groups	Not applicable
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.9 and 6.6 Package Leaflet section 1 and 3 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise physicians' awareness on medication error (prescriber guide and video; in addition, patient guide "Your guide to Vgenfli", and its audio version).

Important potential risk: Off-label use and misuse	
Evidence for linking the risk to the medicine	As with other drugs, Vgenfli might be intentionally used other than recommended, or in clinical conditions outside the approved indications (so-called off-label use). Since the clinical experience with Vgenfli 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 Vgenfli has no dependence potential, the risk of misuse is regarded as very low.
Risk factors and risk groups	Not applicable
Risk minimization measures	Routine risk minimization measures: SmPC section 4.1, 4.3, 4.4 and 4.6 Package Leaflet sections 1, 2 and 3 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on off-label use (prescriber guide and video; in addition patient guide "Your guide to Vgenfli", and its audio version).

Important potential risk: Embryo-fetotoxicity	
Evidence for linking the risk to the medicine	Data from clinical trials, and literature. These toxic effects were thought to be due to the antiangiogenic effect of aflibercept.
Risk factors and risk groups	Patients at risk are women of childbearing potential.

Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4, 4.6 and 5.3 Package Leaflet section 2 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimization measures: Educational program for adults: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on the potential risk of embryo-toxicity and to underline information on treatment of women of child-bearing potential, and the need for appropriate contraception in women of childbearing potential (prescriber guide and video, patient guide "Your guide to Vgenfli", 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 Vgenfli.

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

There are no studies required for Vgenfli.

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 - Specific adverse drug reaction follow-up forms

Annex 4.1: Endophthalmitis and intraocular inflammation (IOI)

SECTION I- REFERENCE ID			
CASE ID:	STUDY ID:		PATIENT ID:
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/lb	Height: unit: kg/lb
SECTION III- PRODUCT INFORMATION			
Therapy date: (dd/mm/yyyy) ☐ ongoing			
Indication:	Number of doses before the event:		
☐ Eye injected/dose: OS ☐2 mg OD ☐2 mg			
In 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		**PSF (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 PSF 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 syringe? ☐ 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 the syringe for injection prepared? ☐ Off-site pharmacy ☐On-site pharmacy ☐Treatment/Examining room			

Vial	PSF (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)	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 in 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 ---- ☐ Related to intravitreal injection procedure ☐ Not related to --- 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 was 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 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- 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 Intraocular pressure increase following the use of Vgenfli 40 mg/mL pre-filled syringe

<table>
<tr><td>Reporter information</td><td>Name:
Email:</td><td colspan="4">_____</td><td colspan="4">☐ Physician ☐ Nurse ☐ Other</td></tr>
<tr><td colspan="3">Istitution Name and address</td><td colspan="3"></td><td colspan="4">Telephone:
Fax:</td></tr>
<tr><td>Patient information</td><td colspan="2">Initials (leave empty for study participants):</td><td colspan="2"></td><td colspan="2">☐ Male
☐ Female</td><td colspan="2">Age (at onset of event)</td><td></td></tr>
<tr><td colspan="2">Product information</td><td colspan="3">Number of doses before the event_____</td><td colspan="3">Dose information:
OS OD
☐ 2.0 mg ☐ 2.0 mg</td><td colspan="2">PSF batch number(s):
Date of expiry:
DD/MM/YYYY</td></tr>
<tr><td colspan="10">Indication:</td></tr>
<tr><td colspan="2" rowspan="2">Adverse event (AE) information</td><td colspan="5">Intraocular Pression (IOP) increase onset date</td><td colspan="4">Last injection date before event onset:</td></tr>
<tr><td>D</td><td>D</td><td>M</td><td>M</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>D</td><td>D</td><td>M</td><td>M</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td colspan="5">Was the IOP value measured pre-injection?
☐ No ☐ Yes, if yes, please provide
• IOP value(s) (mmHg)
• Time/minutes pre-injection and dates
• Method</td><td colspan="5"></td></tr>
<tr><td colspan="5">Was the IOP value measured post-injection?
☐ No ☐ Yes, if yes, please provide
• IOP value(s) (mmHg)
• Time/minutes pre-injection and dates
• Method</td><td colspan="5"></td></tr>
<tr><td colspan="10">How long did the increased IOP last after the injection?</td></tr>
<tr><td colspan="5">Outcome of IOP increase event</td><td colspan="5">☐ recovering/ resolving
☐ recovered/resolved without sequelae
☐ recovered/resolved with sequelae, please detail sequelae:
☐ not recovered/not resolved
☐ unknown</td></tr>
<tr><td colspan="5">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</td><td colspan="5">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):_____)
☐ not applicable</td></tr>
<tr><td colspan="10">Was post injection fundoscopy performed?</td></tr>
</table>

☐ No ☐ Yes, if yes, please provide results of 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	☐ OS ☐ OD ☐ OU Details:
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 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, il yes, please specify the drug names and indications	
Does the patient have any of the following co-morbid conditions (please check all the 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 …….	
PSF details	
Who prepared the --- PSF injection (e.g., physician, nurse, other)? Was the individual specifically trained on the --- PSF? ☐ No ☐ Yes	
Who conducted the – injection with the PSF (e.g., physician, nurse)? Was the individual specifically trained on the --- PSF? ☐ 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 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, have ypu 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	--- ☐ Vial ☐ PFS Other intravitreal injections? ☐
Further notes (free text):	

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable

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

Draft key messages of the additional risk minimisation measures

The following material is provided in this annex:

Vgenfli (Aflibercept) EU Educational Material

The applicant has agreed to provide EU Educational Material for Vgenfli. 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 applicant ensures that, following discussions and agreement with the National Competent Authorities in each Member State where Vgenfli is marketed, ophthalmological clinics where Vgenfli is expected to be used are provided with an updated physician information pack containing the following elements:

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

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

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

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

- Patient information leaflet
- Who should be treated with Vgenfli
- How to prepare for Vgenfli treatment

- What are the steps following treatment with Vgenfli
- 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 Vgenfli

Annex 7 - Other supporting data (including referenced material)

Agard E, Elchehab H, Ract-Madoux G, Russo A, Lagenaite C, Dot C. Repeated intravitreal anti-vascular endothelial growth factor injections can induce iatrogenic ocular hypertension, especially in patients with open-angle glaucoma. Can J Ophthalmol. 2015 Apr;50(2):127–31.

Anderson WJ, da Cruz NFS, Lima LH, Emerson GG, Rodrigues EB, Melo GB. Mechanisms of sterile inflammation after intravitreal injection of antiangiogenic drugs: a narrative review. Int J Retina Vitreous. 2021 May 7;7(1):37.

Bakri SJ, Ekdawi NS. Intravitreal silicone oil droplets after intravitreal drug injections. Retina. 2008;28(7):996–1001.

Bergamo VC, Nakayama LF, Moraes NSBD, Yu MCZ, Höfling-Lima AL, Maia M. Bacterial endophthalmitis following anti-VEGF intravitreal injections: a retrospective case series. Int J Retina Vitreous. 2023 Sep 26;9(1):58.

Carrasco J, Daien V, Eldem BM, Spoorendonk JA, Yoon J. 2-Year Real-World Outcomes with Intravitreal Aflibercept in Neovascular Age-Related Macular Degeneration: Literature Review and Meta-analysis of Patient-Relevant Outcomes. Ophthalmol Ther. 2021 Sep;10(3):397–411.

Chehab HE, Le Corre A, Agard E, Ract-Madoux G, Coste O, Dot C. Effect of Topical Pressure-Lowering Medication on Prevention of Intraocular Pressure Spikes after Intravitreal Injection. European Journal of Ophthalmology [Internet]. 2013 May 1 [cited 2024 Jan 17];23(3):277–83. Available from: https://doi.org/10.5301/ejo.5000159

Chen YX, Li XX, Yoon YH, Sun X, Astakhov Y, Xu G, et al. Intravitreal Aflibercept versus Laser Photocoagulation in Asian Patients with Diabetic Macular Edema: The VIVID-East Study. Clin Ophthalmol. 2020;14:741–50.

Clemens CR, Eter N. Retinal Pigment Epithelium Tears: Risk Factors, Mechanism and Therapeutic Monitoring. Ophthalmologica. 2016;235(1):1–9.

Empeslidis T, Vardarinos A, Konidaris V, Ch'ng SW, Kapoor B, Deane J, et al. Incidence of Retinal Pigment Epithelial Tears and Associated Risk Factors After Treatment of Age-Related Macular Degeneration with Intravitreal Anti-VEGF Injections. Open Ophthalmol J. 2014;8:101–4.

Falavarjani KG, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. Eye (Lond). 2013 Jul;27(7):787–94.

Marticorena J, Romano V, Gómez-Ulla F. Sterile endophthalmitis after intravitreal injections. Mediators Inflamm. 2012;2012:928123.

Mitchell P, McAllister I, Larsen M, Staurenghi G, Korobelnik JF, Boyer DS, et al. Evaluating the Impact of Intravitreal Aflibercept on Diabetic Retinopathy Progression in the VIVID-DME and VISTA-DME Studies. Ophthalmol Retina. 2018 Oct;2(10):988–96.

Okada AA, Takahashi K, Ohji M, Moon SC, Machewitz T, Sasaki K, et al. Efficacy and Safety of Intravitreal Aflibercept Treat-and-Extend Regimens in the ALTAIR Study: 96-Week Outcomes in the Polypoidal Choroidal Vasculopathy Subgroup. Adv Ther. 2022 Jun;39(6):2984–98.

Ohji M, Takahashi K, Okada AA, Kobayashi M, Matsuda Y, Terano Y, et al. Efficacy and Safety of Intravitreal Aflibercept Treat-and-Extend Regimens in Exudative Age-Related Macular Degeneration: 52- and 96-Week Findings from ALTAIR : A Randomized Controlled Trial. Adv Ther. 2020 Mar;37(3):1173–87.

Pielen A, Clark WL, Boyer DS, Ogura Y, Holz FG, Korobelnik JF, et al. Integrated results from the COPERNICUS and GALILEO studies. Clin Ophthalmol. 2017;11:1533–40.

Polizzi S, Mahajan VB. Intravitreal Anti-VEGF Injections in Pregnancy: Case Series and Review of Literature. J Ocul Pharmacol Ther. 2015 Dec;31(10):605–10.

Saito M, Kano M, Itagaki K, Oguchi Y, Sekiryu T. Retinal pigment epithelium tear after intravitreal aflibercept injection. Clin Ophthalmol. 2013;7:1287–9.

Sakai T, Mori C, Ohtsu F. Potential safety signal of pregnancy loss with vascular endothelial growth factor inhibitor intraocular injection: A disproportionality analysis using the Food and Drug Administration Adverse Event Reporting System. Front Pharmacol. 2022;13:1063625.

Santhakumaran S, Salimi A, Brunetti VC, Galic J. Efficacy and Safety of Aflibercept Therapy for Diabetic Macular Edema: A Systematic Review and Meta-Analysis. J Curr Ophthalmol. 2022;34(2):133–47.

Sniegowski M, Mandava N, Kahook MY. Sustained Intraocular Pressure Elevation After Intravitreal Injection of Bevacizumab and Ranibizumab Associated with Trabeculitis. The Open Ophthalmology Journal [Internet]. 2010 Jun 22 [cited 2024 Jan 17];4(1). Available from: https://openophthalmologyjournal.com/VOLUME/4/PAGE/28/ABSTRACT/

Sullivan L, Kelly SP, Glenn A, Williams CPR, McKibbin M. Intravitreal bevacizumab injection in unrecognised early pregnancy. Eye (Lond). 2014 Apr;28(4):492–4.

Stahl A, Sukgen EA, Wu WC, Lepore D, Nakanishi H, Mazela J, et al. Effect of Intravitreal Aflibercept vs Laser Photocoagulation on Treatment Success of Retinopathy of Prematurity: The FIREFLEYE Randomized Clinical Trial. JAMA. 2022 Jul 26;328(4):348–59.

Woo SJ, Bradvica M, Vajas A, Sagong M, Ernest J, Studnicka J, et al. Efficacy and Safety of the Aflibercept Biosimilar SB15 in Neovascular Age-Related Macular Degeneration: A Phase 3 Randomized Clinical Trial. JAMA Ophthalmol. 2023 Jul 1;141(7):668–76.

Annex 8 – Summary of changes to the risk management plan over time

Not applicable