Europe Risk Management Plan

For

Ranluspec

(Ranibizumab 10mg/mL)

(Intravitreal injection in vial and prefilled syringe)

RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data lock point for this RMP: 20 Oct 2025

Date of final sign off: 05 Dec 2025

Rationale for submitting an updated RMP: To update of final approved RMP version

Summary of significant changes in this RMP: Update of final approved RMP version
Other RMP versions under evaluation: No

Details of the currently approved RMP: Not applicable

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List of Abbreviations

ADAs: Anti-Drug Antibodies
AE: Adverse Events
AMD: Age-related Macular Degeneration
AP-ROP: Aggressive Posterior ROP
aRMM: Additional Risk Minimisation Measures
BCVA: Best Corrected Visual Acuity
BRVO: Branch Retinal Vein Occlusion
C1: Complement Factor 1
C2: Complement Component 2
CFB: Complement Factor B
CFH: Complement Factor H
CI: Confidence Interval
CNS: Central nervous system
CNV: Choroidal Neovascularisation
CRVO: Central Retinal Vein Occlusion
CSC: Central Serous Chorioretinopathy
CSDME: Clinically Significant Diabetic Macular Edema
DM: Diabetes Mellitus
DME: Diabetic Macular Edema
DNA: Deoxyribonucleic Acid
DR: Diabetic Retinopathy
DS: Drug Substance
ECG: Electrocardiogram
ELISA: Enzyme-Linked Immunoassay
ETDRS: Early Treatment Diabetic Retinopathy Study
EU-RMP: European Union Risk Management Plan
FA: Fluorescein Angiography
GBD: Global Burden of Disease
GVP: Good Pharmacovigilance Practices
HR: Hazard Ratio
INN: International Non-proprietary Name
IOP: Intraocular Pressure
IP: Investigational Product
IRS: Impurity Reference Standard
IVT: Intravitreal
nAMD: Neovascular age-related Macular Degeneration
NCA: National Competent Authorities
NEI VFQ-25: National Eye Institute Visual Function Questionnaire 25-Item
PDR: Proliferative Diabetic Retinopathy
PDT: Photodynamic Therapy
PFS: Pre-Filled Syringe
PL: Package Leaflet
PM: Pathologic Myopia
RMP: Risk Management Plan
RVO: Retinal Vein Occlusion
SAEs: Serious Adverse Events
SmPC: Summary of Product Characteristics
SPR: Surface Plasmon Resonance
TESAEs: Treatment Emergent Serious Adverse Events

UK:	United Kingdom
US:	United States
VA:	Visual Acuity
VEGF:	Vascular Endothelial Growth Factor
VEGFR:	Vascular Endothelial Growth Factor Receptor
VLBW:	Very Low Birth-Weight

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Ranibizumab
Pharmacotherapeutic group(s) (ATC Code)	Ophthalmologicals, antineovascularisation agents. (ATC code: S01LA04)
Marketing Authorisation Applicant	Lupin Europe GmbH
Medicinal products to which this RMP refers	02
Invented name(s) in Europe	Ranluspec
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Humanised recombinant monoclonal antibody fragment
	Summary of mode of action: Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms (e.g. VEGF110, VEGF121 and VEGF165), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, pathologic myopia and choroidal neovascularisation (CNV) or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to retinal vein occlusion (RVO) in adults.
	Important information about its composition: One ml contains 10 mg ranibizumab*. For Pre-Filled Syringe (PFS): One PFS contains 0.165 ml, equivalent to 1.65 mg ranibizumab. The extractable volume of one PFS is 0.1 ml. This provides a usable amount to deliver a single dose of 0.05 ml containing 0.5 mg ranibizumab. For Vial: Each vial contains 2.3 mg of ranibizumab in 0.23 ml solution. This provides a usable amount to deliver a single dose of 0.05 ml containing 0.5 mg ranibizumab to adult patients. * Ranibizumab is a humanised monoclonal antibody fragment produced in *Escherichia coli* cells by recombinant Deoxyribonucleic acid (DNA) technology.

	Inactive ingredients: Full list of excipients are mentioned in 6.1 of Summary of Product Characteristics (SmPC).
Hyperlink to the Product Information	Please refer SmPC and Package Leaflet (PL).
Product Information	SmPC and PL
Indication(s) in Europe	**Current (if applicable):** <u>Ranibizumab 10 mg/ml solution for injection for vial:</u> **Adults:** • The treatment of neovascular (wet) age-related macular degeneration (nAMD) • The treatment of visual impairment due to diabetic macular oedema (DME) • The treatment of proliferative diabetic retinopathy (PDR) • The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) • The treatment of visual impairment due to choroidal neovascularisation (CNV) <u>Ranibizumab 10 mg/ml solution in pre-filled syringe:</u> **Adults:** • The treatment of neovascular (wet) age-related macular degeneration (AMD) • The treatment of visual impairment due to diabetic macular oedema (DME) • The treatment of proliferative diabetic retinopathy (PDR) • The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) • The treatment of visual impairment due to choroidal neovascularisation (CNV)
	Proposed (if applicable): Not applicable
Dosage in Europe	**<u>Current:</u>** Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections. **<u>In adults:</u>** The recommended dose for ranibizumab in adults is 0.5 mg given as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml. The interval between two doses injected into the same eye should be at least four weeks.

	Treatment in adults is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD, DME, PDR and RVO, initially, three or more consecutive, monthly injections may be needed. Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters. If patients are being treated according to a treat-and-extend regimen, once maximum visual acuity is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval should be extended by no more than two weeks at a time for wet AMD and may be extended by up to one month at a time for DME. For PDR and RVO, treatment intervals may also be gradually extended, however there are insufficient data to conclude on the length of these intervals. If disease activity recurs, the treatment interval should be shortened accordingly. **The treatment of visual impairment due to CNV** should be determined individually per patient based on disease activity. Some patients may only need one injection during the first 12 months; others may need more frequent treatment, including a monthly injection. For CNV secondary to pathologic myopia (PM), many patients may only need one or two injections during the first year. **Ranibizumab and laser photocoagulation in DME and in macular oedema secondary to Branch Retinal Vein Occlusion (BRVO)** There is some experience of Ranibizumab administered concomitantly with laser photocoagulation. When given on the same day, Ranibizumab should be administered at least 30 minutes after laser photocoagulation. Ranibizumab can be administered in patients who have received previous laser photocoagulation.
	Proposed (if applicable): Not Applicable
Pharmaceutical form(s) and strengths	**Current:** Form: Solution for Intravitreal injection in vial and prefilled syringe Strength: 10mg/mL

	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the Europe?	Yes

Part II: Safety specifications

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

Ranibizumab is indicated in adults for the treatment of:

- Neovascular (wet) age-related macular degeneration (AMD)
- Visual impairment due to choroidal neovascularisation (CNV)
- Visual impairment due to diabetic macular oedema (DME)
- Visual impairment due to macular oedema secondary to retinal vein occlusion (RVO) (branch RVO or central RVO)
- Proliferative diabetic retinopathy (PDR)

1. Neovascular (wet) age-related macular degeneration (AMD)[1]

AMD, the progressive degenerative macular disease has 2 major forms, commonly referred to as dry and wet, primarily differentiated by the presence or absence of a neovascular (wet) component, although both forms can occur in the same patient. The neovascular form of the disease usually causes severe vision loss and is characterized by the abnormal growth of new blood vessels under or within the macula, the central portion of the retina responsible for high-resolution vision.

Incidence:

Table SI 1: Incidence of AMD in European region

Country	Study period	No. of patients	Mean age (y)	Cumulative incidence (%)	Reference
Iceland	2002-2011	2196	75 ± 5	0.7	Jonasson et al.2014[2]
Netherlands, United States (US), Australia,	1988-1999	9,523	63	1.1	Tomany et al.2004[3]
Denmark	1986-2022	359	68	14.8	Buch et al 2005[4]

Prevalence[1]:

The prevalence of nAMD increases with age. In a pooled analysis of three population-based studies from three continents, the prevalence of nAMD increased from 0.17% among subjects aged 55 to 64 years to 5.8% for those older than 85 years. Another analysis on six studies in the US, Australia and Europe estimated a pooled prevalence of nAMD of 1.05% (95% Confidence Interval (CI): 0.57-1.52) for subjects aged 65-79 years. It is estimated that prevalence of nAMD is 1.2% (95% CI: 0.9-1.7) in United Kingdom (UK) and 0.3% (95% CI: 0.1-0.5) in Republic of Ireland for subjects aged ≥50 years. Further, in the Denmark, Norway and Sweden estimated a pooled prevalence of nAMD of 3.61% for subjects aged 65 years.

Demographics of the population in the proposed indication and risk factors for the disease[1]:

Risk of nAMD steeply increases with age. It is more common in Asian or White patients compared to Blacks. Environmental and behavioral factors includes cigarette smoking, obesity, low dietary intake of vitamins A, C, and E, and zinc, omega-3 fatty acids, unhealthy lifestyle related to cardiovascular risk factors. Ocular risk factors are darker iris pigmentation, history of cataract surgery, hyperopic refraction. Some genetic loci like complement factor H (CFH), complement factor B (CFB), complement component 2 (C2), complement factor 1 (CF1) etc.

The main existing treatment options[1]:

Anti-VEGF therapies delivered intravitreally are the main therapies used for treatment of neovascular AMD and include ranibizumab and aflibercept (Eylea, Bayer/Regeneron). Additionally, bevacizumab (Avastin, Genentech/ Roche) is unlicensed for ocular use yet broadly used in clinical practice worldwide. Photodynamic therapy with verteporfin is also licensed in this indication although use in clinical practice is limited as is use of laser for extrafoveal lesions.

Natural history of the indicated condition in untreated population, including mortality and morbidity[1]:

Untreated nAMD is associated with a risk of impaired vision, including blindness. A study in the US Medicare database followed a cohort of patients newly diagnosed with any AMD between 1994 and 2004 (before anti-VEGF treatments became available). The 10-year cumulative incidences of blindness, severe vision loss and moderate vision loss in this cohort were 3.2%, 5.4% and 6.0%, respectively; there was a statistically significant 2.3-fold increase in blindness and 3.7-fold increase in severe vision loss when compared to the control population without AMD.

Mortality: Decreased visual acuity (VA) is associated with increased five-year mortality and even relatively mild visual impairment increases the risk of death more than two-fold. nAMD was reported as a significant risk factor for all-cause mortality in women in a population-based 14-year cohort study in people aged 60 - 80 years in Denmark and in men only in a 15-year cohort study in Australia. In a cohort study in Iceland, nAMD was associated with all-cause mortality only in the subgroup aged 83 years or older, while in the beaver dam eye study, nAMD was significantly associated with all-cause mortality only among persons younger than 75 years.

Important co-morbidities[1]:

The most common co-morbidities found in patients with nAMD are Cataract, Glaucoma, Hypertension, Hyperlipidemia, Diabetes, Myocardial Infarction, Stroke, Depression, Anxiety.

2. Diabetic Macular Edema (DME)

Incidence:

Table SI 2: Incidence of DME in European region

Country	Study period	No. of patients	Mean age (y)	Cumulative incidence (%)	Reference
Type 1 Diabetes					
Finland	1997-2009	1354	38.7±11.6	0-4 years- 17 5-15 years- 27 15-40 years- 34	Hietala et al 2013[5]
Spain	2000-2009	334	25.17 ±11.74	11.07	Romero- Aroca et al 2011[6]
Sweden	1990-1993	294	34.1	2.4	Henricsso n et al 1999[7]
Type 2 Diabetes					
Sweden	1990-1993	1291	60.9	On insulin: 4.5 No insulin: 1.4	Henricsso n et al 1999[7]
Any type of Diabetes					
United Kingdom	2000-2007	64,983	34.0 (Type 1 Diabetes), 62.8 (Type 2 Diabetes)	18	Martin- Merino et al 2014[8]

Prevalence:

Table SI 3: Prevalence of DME in European region

Country	Study period	No. of patients	Prevalence (%)	Reference
Type 1 Diabetes				
Finland	1997-2009	1354	18	Hietala et al 2013[5]
Sweden	1990-1993	404	17	Henricsso n et al 1999[7]
Type 2 Diabetes				
Spain	2008-2012	108,723	0.18	Rodriguez- Poncelas et al 2015[9]
Germany, Austria,	2000-2013	64,784	0.8	Hammes et al 2015[10]
Any type of Diabetes				
United Kingdom	2007-2010	48,450	13.9	Keenan et al 2013[11]

Demographics of the population in the proposed indication and risk factors for the disease[1]:

The key factor in the development of DME is diabetes duration, age, black ethnicity, HbA1c and total cholesterol levels.

The main existing treatment options[1]:

Currently, ranibizumab and aflibercept, anti-VEGF therapies, are approved for the treatment of visual impairment due to DME. Other treatments used include laser retinal photocoagulation, the intravitreal (IVT) administration of steroids or the use of IVT steroid-releasing implants.

Natural history of the indicated condition in untreated population, including mortality and morbidity[1]:

DME is a frequent manifestation of Diabetic retinopathy (DR), and is a leading cause of legal blindness in diabetics. Presence of DME has been associated with a doubling of the visual angle and loss of vision. A review of the published literature showed that DME was associated with a reduction in the quality of life of the affected patients. In the UK DR Screening Service for Wales dataset (2004-2005), Clinically Significant Diabetic Macular Edema (CSDME) resulting in sight loss (blindness and impaired vision) was present in 2.75% (95% CI: 2.56-2.95) of 27,178 diabetes patients; 2.64% (95% CI: 2.45-2.84) CSDME resulting in impaired vision and 0.11% (95% CI: 0.07-0.157) blindness attributable to DME.

Mortality: Decreased VA is associated with increased five-year mortality and even relatively mild visual impairment increases the risk of death more than two-fold.

Important co-morbidities[1]:

The most common co-morbidities found in patients with DME are Cataract, Glaucoma, Hypertension, Hyperlipidemia, Nephropathy/ proteinuria, Myocardial Infarction, Stroke.

3. Retinal Vein Occlusion

Incidence[1]:

There are two types of ROV, branch RVO (BRVO) and central RVO (CRVO). The cumulative incidence of RVO ranged between 0.8% and 3.0% in different populations, depending on the years of follow-up and the average age of the studied population. The incidence of BRVO appeared to be consistently higher than of CRVO.

Prevalence[1]:

The overall prevalence of RVO in various populations usually is reported between 0.3% and 2%, with a BRVO to CRVO ratio between 3:1 and 8:1; a recent review article estimated that BRVO is 4 to 6 times more prevalent than CRVO.

A pooled analysis was conducted that included the original data from published studies reporting RVO prevalence and unpublished data. In total 15 studies were included, with 68,751 subjects and 555 RVO cases. In this pooled analysis, the prevalence of RVO was

estimated at 0.44%, with the prevalence of CRVO lower at 0.06%. In the individual studies, the prevalence of RVO was between 0.3% and 1.6%, and that of BRVO and CRVO were between 0.25%-1.1% and 0.05%-0.4%, respectively. A total of 5% to 11% of patients had bilateral involvement.

Demographics of the population in the proposed indication and risk factors for the disease[1]:

The mean age of RVO patients ranged from 49 to 67 years in epidemiological studies assessing its prevalence.

The ethnicity of patients with RVO was assessed in a pooled analysis showed that prevalence of RVO according to race was Whites: 0.37% (0.28%-0.46%), Blacks: 0.39% (0.18%-0.60%), Asians: 0.57% (0.45%-0.68%), Hispanics: 0.69% (0.57%-0.83%).

The risk factor in the development of RVO are advancing age, hypertension, arteriosclerosis, diabetes mellitus, hyperlipidemia, vascular cerebral stroke, blood hyperviscosity, and thrombophilia, metabolic syndrome, end-organ damage caused by diabetes mellitus and hypertension, American black ethnicity, Female sex, Congenital thrombophilic diseases, Cigarette smoking, ocular hypertension and glaucoma, higher ocular perfusion pressure, and changes in the retinal arteries.

The main existing treatment options[1]:

Current treatments available for the management of retinal vein occlusion include: laser photocoagulation, intravitreal steroids such as triamcinolone acetonide, intravitreal steroid releasing implants such as fluocinolone (Iluvien®) and dexamethasone (Ozurdex®) (Kiire and Chong 2012). Ranibizumab and aflibercept, anti-VEGF therapies, are approved for the treatment of visual impairment due to macular edema associated with a retinal vein occlusion.

Natural history of the indicated condition in untreated population, including mortality and morbidity[1]:

RVO is a frequent cause of eye disease in the middle aged and elderly. It may lead to severe vision loss from macular edema, macular ischemia, and vitreous hemorrhage. One paper evaluating the vision-related quality of life in patients with CRVO showed that this condition was associated with a decreased quality of life related to the degree of visual loss in the better- seeing eye and the overall systemic health of the patient. One recent study showed that BRVO is associated with a decreased vision-related quality of life that correlated with the involved eye VA, even when the uninvolved eye maintained good VA.

Table SI 4: All-cause, cardiovascular mortality in patients with RVO

Country	Study period	No.of patients	Age (Y)	Mortality rate (%)		Reference
				All cause	Cardiovascular	
Singapore	2004-2006	3280	40-80	30.4	26.9	Siantar et al 2015[12]
Denmark	1976-2010	439	60	5.9	-	Bertelsen et al 2014[13]

Country	Study period	No.of patients	Age (Y)	Mortality rate (%)		Reference
				All cause	Cardiovascular	
China	2000-2007	44	< 40	9.1	-	Kuo et al,2010[14]

Important co-morbidities[1]:

The most common co-morbidities found in patients with RVO are Cataract, Glaucoma, Hypertension, Hyperlipidemia, Diabetes, Myocardial Infarction, Stroke, Coagulopathies.

4. Choroidal neovascularization (CNV)

Incidence and Prevelance[1]:

Epidemiology of CNV due to causes other than nAMD is challenging to describe, as in many conditions CNV has only been reported in individual case reports, with no data on the frequency of their occurrence. Some conditions, which may be complicated by CNV, are by themselves very rare, so the incidence and prevalence estimates are not always available. Finally, the frequency and characteristics of the underlying conditions often vary across ethnicities and geographical areas. Therefore, the following section provides the incidence and prevalence of specific underlying conditions, and a proportion of patients that have been reported to eventually progress to CNV. No attempt is made to provide an exhaustive list of all conditions that have been associated with CNV; instead, the focus is on the main subtypes described in the literature:

CNV secondary to pathologic myopia (PM)

Incidence: A study using nationwide health insurance records in Taiwan found that incidence of new CNV secondary to PM was 11.9 per 100,000 (95%CI 11.4-12.4) in 2010 and 12.5 per 100,000 (95% CI 12.0-13.0) in 2011.

Prevalence: The prevalence of myopic CNV among adults in the United States was estimated at 0.017%. A study in Taiwan (2009-2011) provided the same prevalence estimate of 0.017%.

Idiopathic CNV

A proportion of CNV cases either cannot be attributed to a known etiology or the associated etiology has not yet been identified. This proportion in most studies was between 11 and 17%. In one US study 39% of peripapillary subretinal neovascular membranes were reported as idiopathic. There are no reports of the incidence and prevalence of idiopathic CNV. The initial diagnosis may be reclassified upon application of further diagnostic tools or as the underlying disease manifests with time. For instance, one study reported that 7% (4/58) of patients initially diagnosed with idiopathic CNV eventually were discovered to have various inflammatory chorioretinal diseases of the white dot syndrome spectrum.

CNV secondary to angioid streaks

Angioid streaks are most often associated with pseudoxanthoma elasticum. Most studies of CNV secondary to angioid streaks report prevalence of pseudoxanthoma elasticum of 40%-80%; remaining cases usually cannot be attributed to a known cause. Other underlying systemic diseases associated with angioid streaks such as sickle cell disease are reported rarely, mainly in areas of increased risk.

CNV secondary to intraocular inflammation

In the studies conducted in Europe and North America, the incidence of uveitis at any anatomical location was between 25 and 52 per 100,000 persons per year, and the prevalence was between 70 and 145 per 100,000 persons.

CNV secondary to Central serous chorioretinopathy (CSC)

Incidence: A study using linked medical records in Olmsted county, Minnesota, US (1980-2002) reported mean age-adjusted annual incidence of CSC of 9.9 (95% CI: 7.4-12.4) per 100,000 in men and 1.7 (95% CI: 0.74-2.7) in women. A study in the Taiwan National Health Insurance database (2001-2006) reported a mean annual incidence of 27 per 100,000 in men and 15per 100,000 in women.

Prevalence (underlying condition): estimates not found.

Proportion developing CNV: Retrospective medical records review from a tertiary center in Italy (2008-2013) found CNV in 41/272 (15%) eyes of 136 patients, followed for a mean 14±12 months. However, a retrospective case series in Miami, US (1970-1997) found CNV in only 2/101 eyes (2%) followed for a mean of 10 years.

CNV secondary to other causes - choroidal nevi

Incidence (underlying condition): estimates not found.

Prevalence (underlying condition): In the US National Health And Nutrition Examination Survey 2005-2008, the prevalence of choroidal nevus among 5575 participants aged 2:40 years was 4.7%. In the US Multi-Ethnic Study of Atherosclerosis (2002-2004, 6176 persons) prevalence of choroidal nevi was 2.1%. In the Australian Blue Mountains Eye Study (1992-1994) prevalence was 6.5%. In the Beijing Eye Study (2001) prevalence of choroidal nevi in 4277 participants was 2.9%±0.3% per subject or 1.5%±0.1% per eye.

CNV secondary to other causes – other ocular tumours

Various benign and malignant ocular tumors have been associated with CNV in the literature. The age-adjusted incidence of all malignant ocular tumors in the US and England (UK) in 2003-2007 did not exceed 1 per 100,000 persons per year. Individual estimates of the incidence and prevalence of benign ocular tumors other than choroidal nevi were not found.

CNV secondary to other causes – Choroidal trauma

Incidence (underlying condition): In Scotland (1991-1992), the annual cumulative incidence of ocular trauma hospital admission was 8.1 per 100,000 populations (95% CI:

7.4-9.0); a follow-up study in 2008-2009 reported a lower incidence of about 2 per 100,000. A study in Sicily, Italy (2001-2005) found that the incidence of eye injuries leading to hospitalization was 4.9 per 100,000. In Sardinia, Italy (1993- 2004) the annual incidence of hospitalizations due to ocular trauma was 3.2 per 100,000.

Prevalence (underlying condition): Prevalence estimates for choroidal rupture were not found. Some studies report lifetime prevalence of any ocular injuries to be as high as 10-20%, however, only a very small proportion of those would result in choroidal rupture.

CNV secondary to other causes – inherited retinal dystrophies

Incidence: In UK, the annual cumulative incidence of inherited retinal dystrophies associated with CNV in patients with Stargardt disease was 0.11 per 100,000 populations and in patient with best disease it was 0.035

Prevalence: In UK, cumulative prevalence of inherited retinal dystrophies associated with CNV in patients with Stargardt disease was 10-12.5 per 100,000 person and in patient with best disease it was 1.5.

Demographics of the population in the proposed indication and risk factors for the disease:

Risk factors for the disease: The information on the risk factors of developing CNV secondary to etiologies other than nAMD is relatively scarce.

Pathologic myopia: Although there are risk factors known for the development of PM, there is still little information on the cause of the condition.

Main risk factors identified:

- High Myopia
- Female gender
- Ethnicity: higher risk among Asians and lower among Africans and Pacific Islanders

  Strong genetic basis as shown by twin studies. Several association studies have identified some candidate genes but most of the genetic association remains to be elucidated.

Idiopathic: Apart from female gender, which was identified as a risk factor in a number of studies, there exists no definite information on specific risk factors for the development of idiopathic CNV. One study in Japan noted that patients with idiopathic CNV were significantly more likely to have high myopia (in absence of myopic retinopathy) than community-sampled controls without CNV. Angioid streaks: Patient age has been reported as the main risk factor for CNV development. Width, length and location of the angioid streaks seem to also play a role: the wider and longer are the angioid streaks the higher the risk for CNV, especially if the lesions are located in a distance less than one optic disc diameter from the foveola. In addition, even mild head injuries are a risk factor for the breaks in the Bruch's membrane.

Inflammation: A large study looking at 15,137 uveitic eyes (8868 patients) found that CNV was rare in the cases of anterior or intermediate uveitis. Risk factors for CNV at presentation included posterior uveitis in general and specific uveitis syndromes affecting the outer

retina- retinal pigment epithelium-choroid interface. Risk factors for incident CNV included currently active inflammation (adjusted Hazard Ratio (HR), 2.13; 95% CI: 1.26-3.60), preretinal neovascularization, HR=3.19 (95% CI: 1.30-7.80), and prior diagnosis of CNV in the contralateral eye, HR=5.79 (95% CI: 2.77-12.09). Among specific syndromes, the incidence was greater in Vogt-Koyanagi- Harada syndrome, HR=3.37 (95% CI: 1.52-7.46) and punctate inner choroiditis, HR=8.67 (95% CI: 2.83-26.54). Smoking has also been reported as a risk factor for CNV development in ocular histoplasmosis.

Central serous chorioretinopathy: No information has been identified on the risk factors predisposing to CNV development in CSC. The main risk factors for CSC include systemic corticosteroid use, male gender, type A personality, pregnancy, endogenous Cushing's syndrome, and acute stress.

Other causes: A retrospective review of 17 patients with CNV secondary to choroidal nevi and literature case review concluded that CNV is not associated with the nevus size, may be of variable type and location, and is not associated with malignant transformation, but on the contrary, may be associated with a benign nature of a melanocytic lesion. The main risk factor for choroidal nevi in general is White race, which confers 10-fold higher risk than in Blacks and 2-fold higher than in Hispanics.

A study in 74 eyes of 61 patients with choroidal osteoma found that the following factors were associated with development of CNV in a univariate analysis: presence of symptoms, irregular surface of tumor (vs. smooth), VA 20/40 at initial examination, hemorrhage on tumor, yellow color of tumor (vs. orange) and presence of subretinal fluid. In a multivariate analysis, only irregular surface of tumor, RR=l0.6 (95% CI 1.1-98.6) and hemorrhage on tumor, RR=15.1 (2.4-93.2) remained significant factors.

A study in the US evaluating 111 patients with traumatic choroidal ruptures found that older age and location of rupture within the arcades were positively associated with CNV formation.

The main existing treatment options:

Current treatments available for the management of CNV are Submacular surgery, Laser photocoagulation, Photodynamic therapy, Corticosteroids or other immunosuppressants (eg: intravitreal triamcinolone acetonide), Anti-VEGF agents.

Natural history of the indicated condition in untreated population, including mortality and morbidity[1]:

Morbidity associated with CNV with the underlying etiologies other than nAMD varies depending on the condition. Pathologic myopia remains a common cause of blindness and visual impairment in various countries. In a study in Italy, degenerative myopia was the cause of 10.5% of all binocular blindness and 3.2% of all monocular blindness, although results were based on small numbers. A study in Spain found that the prevalence of PM in elderly blind patients and visually impaired patients was 23.3% (95% CI: 11.75-38.63) and 12% (95% CI: 6.12- 20.38), respectively. In a study in Netherlands, myopic degeneration was the underlying cause of visual impairment in 6% of the elderly blind population and 6% of visually impaired population. A number of studies that observed untreated idiopathic CNV

cases concluded that the visual prognosis in such patients is better than may be expected in nAMD, with a majority of patients retaining useful vision after a few years of follow up. However, observational studies of treatment with VEGF inhibitors in this patient population report a significant and sustained improvement in visual acuity.

CNV secondary to angioid streaks is a vision-threatening complication; earlier studies reported that as many as 50% of patients may progress to legal blindness (VA <1/20) if left untreated. CNV is one of the most severe complications in uveitis of different etiologies, and when untreated often leads to permanent and severe visual impairment. Acute CSC resolves spontaneously in most cases, however, CNV may occur at any time after the initial diagnosis and is associated with poor visual outcome. Development of CNV is a major cause of visual loss in choroidal osteoma and a risk factor for decreased vision in patients with choroidal nevi.

Mortality: No specific data on the mortality in patients with CNV of etiologies other than nAMD has been found in literature. However, on a general note, decreased visual acuity has been associated with increased five-year mortality and even relatively mild visual impairment increases the risk of death more than two-fold.

Some systemic conditions associated with CNV may confer increased mortality; e.g. patients with sickle-cell anemias are at increased risk of death from infections, stroke, acute chest syndrome, heart disease and other complications. Systemic inflammatory conditions may be also associated with increased mortality, e.g. patients with sarcoidosis have increased risk of death due to cardiomyopathy or other complications. Patients with Behçet's disease and cardiac involvement (between 7% and 46%) have poorer survival than those without; in a retrospective study in China (1995-2010) 102 of 796 patients with Behçet's disease (mean age 34 years) demonstrated vascular lesions; of those, 4 died during follow-up from arterial aneurysms rupture.

Important co-morbidities[1]:

The most common co-morbidities found in patients with CNV are Cataract, Glaucoma, Macular edema, Hypertension, Coronary heart disease, Myocardial Infarction, Stroke, Renal disease.

5.Diabetic Retinopathy (DR)

Incidence[1]:

Table SI 1: Incidence of DR in European region

Country	Study period	No. of patients	Mean age (y)	Annual incidence rate, per 100 (95%CI)	Reference
Type 1 Diabetes					
Spain	2000-2009	334	25.2	3.6	Romero-Aroca et al 2011)[6]

Country	Study period	No. of patients	Mean age (y)	Annual incidence rate, per 100 (95%CI)	Reference
Type 2 Diabetes					
UK,Wales	2005-2009	49,763	64.4	1st year: 12.5 4th year: 6.7	Thomas et al 2012[15]
Spain	2007-2011	2,405	67.5	2.4	Salinero-Fort et al 2013)[16]
Portugal	2009-2014	30,641	70	1st year: 4.6 5th year: 3.9	Dutra Medeiros et al 2015)[17]
Any Diabetes					
UK	2006-2007	19,569	59.4	4.8	Martin-Merino et al 2014)[18]

Prevalence[1]:

A recent meta-analysis collated data from 22,896 individuals with diabetes from 35 studies in the US, Australia, Europe, and Asia. Age-standardized prevalence of any DR in individuals with Diabetes Mellitus (DM) aged 20-79 was 35.4% (95% CI: 35.2-35.6), and prevalence of vision threatening DR was 11.7% (95% CI: 11.6-11.8) when analysis was limited to studies with similar methodologies and rigorous outcome definitions.

Demographics of the population in the proposed indication and risk factors for the disease[1]:

In a recent meta-analysis that summarized data from US, Australia, Europe, and Asia, prevalence of DR across both diabetes types was slightly higher in men, compared to women: 36.3% (95% CI: 36.0-36.6) in men and 34.5 (95% CI: 34.2-34.7) in women.

The risk of DR was the greatest in Black (African American) diabetes patients with prevalence of 49.6% (95%CI 48.6--50.5), followed by Caucasian and Hispanic patients: 45.8% (95%CI 45.4-46.1) and 34.6% (95%CI 33.2-35.9), respectively. In contrast, prevalence of DR in Chinese patients was 25.1% (95%CI 24.3-25.9) and in South Asian patients it was as low as 19.1% (95%CI 18.9-19.4). Similar trend was observed for STDR.

DR is positively associated with other microvascular complications of diabetes, such as peripheral and autonomous neuropathy and nephropathy. A recent study concluded that presence of diabetic polyneuropathy increases risk of DR more than 5-fold (HR=5.41; 95%CI 4.92-5.94) even after adjustment for age, sex, diabetes duration, nephropathy and other comorbidities.

The key factors in the development of DR are poor glycemic control, prolonged diabetes duration, diabetic drug use, obesity, hypertension, hyperlipidemia, male sex, chronic kidney disease, smoking, myopia and pregnancy.

The main existing treatment options[1]:

Anti VEGF therapy, Panretinal photocoagulation and Vitreous surgery.

Natural history of the indicated condition in untreated population, including mortality and morbidity[1]:

A systematic review and meta-analysis of published and unpublished population-based data for the causes of vision impairment and blindness from 1980 to 2014 had included 3,983,541 participants from 98 countries. It concluded that among the global population with moderate or severe vision impairment in 2015 (estimated as 216.6 million with 80% uncertainty interval 98.5 to 359.1 million), DR was the fifth leading cause after uncorrected refractive error, cataract, age-related macular degeneration and glaucoma. It was estimated to cause 2.6 million cases of vision impairment and blindness globally in 2015 (80% uncertainty interval 0.2 to 9.9 million). By 2020, among the global population with moderate or severe vision impairment, the number of people affected by DR is anticipated to rise to 3.2 million (0.2 to 12.9 million).

Mortality: Multiple studies have evaluated association between DR and all cause and cardiovascular mortality. A meta-analysis that included 20 studies providing data from 19,234 diabetes patients concluded that in patients with type 2 diabetes (n = 14,896), the presence of any degree of DR increased the chance for all-cause mortality and/or Cardiovascular events by 2.34 (95%CI 1.96-2.80) compared with patients without DR. In patients with type 1 diabetes (n = 4,438), the corresponding odds ratio was 4.10 (95% CI: 1.50-11.18). These associations remained after adjusting for traditional Cardiovascular risk factors. DR was also predictive of all-cause mortality in type 2 diabetes (OR=2.41; 95%CI 1.87-3.10) and type 1 diabetes (OR=3.65; 1.05-12.66).

Another meta-analysis concluded that DR was associated with higher risk of all-cause mortality in patients with both type 2DM (RR=2.25, 95% CI 1.91-2.65) and type I DM (RR=2.68, 95% CI 1.34- 5.36). Risk of all-cause mortality varied according to different grades of DR in patients with type 2 DM; the risk increase in patients with NPDR was 1.38 (95%CI 1.11-1.70), while the risk in PDR was 2.32 (1.75-3.06).

Important comorbidities[1]:

The key comorbidities in the population with DR are Cataract, Glaucoma, Macular edema, Hypertension, peripheral neuropathy, proteinuria, chronic kidney disease, Hyperlipidemia, Myocardial Infarction and Stroke or transient ischemic attack.

6

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

Key safety findings from non-clinical studies and relevance to human usage:

Lupin Ranibizumab is proposed similar biologics to the Lucentis®. The non-clinical study of Lupin's similar biologics Ranibizumab was conducted in rabbit. Since this species is

considered as non-relevant, pharmacodynamics and pharmacodynamics evaluation was not conducted in non-clinical study. However, Lupin has conducted 28-Day intravitreal toxicity study of ranibizumab in rabbit with 14-day recovery period.

Part II: Module SIII - Clinical trial exposure

Lupin developed a test formulation Lupin Ranibizumab as a biosimilar product to the innovator product Lucentis® (Ranibizumab), which has been studied in various Phase I to IV clinical studies. Lucentis® is approved and available in the market globally, since 2006. Below presented clinical studies were conducted by Lupin to demonstrate the biosimilarity between Lucentis® and Lupin Ranibizumab in terms of efficacy, safety, and immunogenicity.

Following data represents exposure to Lupin Ranibizumab.

Table SIII.1: Subjects Exposure to study drug (cumulative)

Population	Lupin Ranibizumab (Ranibizumab) (n)	Comparator Lucentis® (n)
Patients with Neovascular Age-Related Macular Degeneration	410	412

Overall Lupin Ranibizumab /Lupin`s Ranibizumab was well tolerated and the safety profile was similar with the marketed product Lucentis®. Majority of the AEs were mild or moderate in severity and was comparable between both the treatment groups. Severe AEs and SAEs were reported for a minority of subjects across trials. TEAEs leading to discontinuation of study drug occurred with similar frequency in both treatment groups. No new safety concern was identified following the treatment.

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

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

In study LRP/LUBT010/2016/008 subjects were excluded from the study if they met any of the following criteria:

a) Known hypersensitivity to Ranibizumab or any of the components of the study medication.
b) Known history of allergy to fluorescein dye.
c) Scar, fibrosis, or atrophy involving the center of the fovea in the study eye as assessed by Fluorescein Angiography (FA) (confirmed by independent central reading center).

d) Subretinal hemorrhage in the study eye that involved the center of the fovea, the size of the hemorrhage was either ≥50% of the total lesion area or ≥1-disc area (DA) in size (confirmed by independent central reading center).
e) Total lesion area ≥12.0-DA in size (including blood, scars, and neovascularization) as assessed by FA in the study eye (confirmed by independent central reading center).
f) History of vitrectomy, sub-macular surgery, or other surgical intervention for AMD in the study eye.
g) Employees of clinical study sites, individuals directly involved with the conduct of the study or immediate family members thereof, prisoners, and persons who were legally institutionalized.
h) Any other pathology involving the CNV lesion like retro-foveolar atrophy or permanent structural damage to fovea or fibrosis/ hemorrhage involving fovea >50% of lesion area of study eye that could have affected the efficacy of the study medication.
i) Vitreous hemorrhage or history of rhegmatogenous retinal detachment, retinal pigment epithelial tears or rips involving the macula or macular hole (Stage 1 to 4) in the study eye as assessed by FA (confi
j) rmed by independent central reading center).
k) Uncontrolled glaucoma as evident by progressive damage to optic nerve or visual fields despite optimum therapy; or steroid-induced glaucoma with continued use of steroids that required intraocular pressure (IOP) lowering treatment.
l) History of serious complications following surgery in the study eye within 1 year prior to randomization.
m) Previous treatment with intravenous or intravitreal anti-VEGF agents such as bevacizumab, ranibizumab, aflibercept, pegaptanib, brolucizumab in either of the eyes.
n) Previous external beam radiation or any laser therapy photocoagulation/thermal laser thermotherapy/verteporfin photodynamic therapy (PDT) involving the foveal center in the study eye within 5 years prior to randomization.
o) Previous treatment with verteporfin PDT, thermal laser, transpupillary thermotherapy (except subfoveal) in the study eye or use of protein kinase C inhibitors within 3 months prior to randomization.
p) Previous treatment with intravitreal steroids (eg, triamcinolone, anecortave acetate) in the study eye within 3 months prior to randomization.
q) Previous treatment with intravitreal steroid implant (eg, Ozurdex®) within 6 months prior to randomization.
r) Concurrent use of systemic anti-VEGF agents.
s) Intraocular surgery (including cataract surgery) in the study eye within 3 months prior to randomization.
t) Concurrent treatment with an investigational drug or device in the non-study eye.
u) Previous participation in any study of investigational drugs within 30 days or as prescribed in that study (whichever was later) preceding the initial study treatment.
v) Patients with diabetic macular edema and/or background or proliferative retinopathy were excluded. Likewise, any patient with significant posterior subcapsular cataract was also excluded.
w) Choroidal neovascularization in the study eye due to causes other than AMD such as histoplasmosis, trauma, or pathological myopia etc, or CNV lesion not likely to respond to ranibizumab.

x) Active or ongoing ocular infection (eg, infectious conjunctivitis, keratitis, scleritis, or endophthalmitis) or severe inflammation in either of the eyes.
y) Any concurrent intraocular condition in the study eye that could have either required medical or surgical intervention during the 12-month study period or that could have contributed to a loss (of at least 2 Snellen equivalent lines) of BCVA over the 12 months study period (eg, progressive retinal disease or retinal pathology, cataract, glaucoma, uveitis, previous corneal transplant, the refractive error more than -8 diopters of myopia etc.). The decision regarding exclusion was to be based on the opinion of the Investigator.
z) Any patient with cloudy media from any cause, that prevented adequate visualization of the fundus with indirect ophthalmoscopy were excluded.
aa) Patients with seropositivity for hepatitis B, hepatitis C, human immunodeficiency virus antibody, syphilis tests or any immunodeficiency and/or immunosuppressive disease or active systemic infection.
bb) History or presence of concurrent systemic diseases or dysfunctions requiring significant medical/surgical intervention during study period that might have affected interpretation of the results or contraindicated the use of ranibizumab or rendered the patient at high risk for treatment complications based on the Investigator's judgment such as: Cardiovascular disease (eg, stroke, myocardial infarction), uncontrolled respiratory, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic (eg, optic neuropathy), metabolic, pulmonary, autoimmune disease or psychiatric disease based on previous history and relevant reports of clinical examination, laboratory tests, or ECG etc.

In study LRP/RBZ/2015/002 subjects were excluded from the study if they met any of the following criteria:

1. Any other pathology involving the CNV lesion like retrofoveolar atrophy or permanent structural damage to fovea or fibrosis/ hemorrhage involving fovea > 50 % of lesion area of study eye that could affect the efficacy of drug.
2. Vitreous hemorrhage or history of rhegmatogenous retinal detachment, retinal pigment epithelial tear involving the macula or macular hole (stage 3 or 4) in the study eye.
3. Aphakia or absence of the posterior capsule in the study eye.
4. Uncontrolled glaucoma as evident by progressive damage to optic nerve or visual fields despite optimum therapy; or steroid-induced glaucoma with continued use of steroids that requires IOP-lowering treatment.
5. History of o serious complications following surgery in the study eye within 1 year prior to randomization.

Concomitant Medications/ Treatments & Procedures:

6. Previous treatment with intravenous Bevacizumab (Avastin®), or intravitreal Ranibizumab (Lucentis®), Bevacizumab (Avastin®), Aflibercept (Eylea®), Pegaptanib (Macugen®) in either of the eyes.

7. Previous external beam radiation or subfoveal focal laser photocoagulation/ thermal laser or transpupillary thermotherapy in the study eye within 5 years prior to randomization.
8. Previous treatment with verteporfin photodynamic therapy (PDT), thermal laser, transpupillary thermotherapy, intravitreal or protein kinase C inhibitors or other AMD therapy in the study eye within 3 months prior to randomization.
9. Previous treatment with intravitreal ocular or periocular steroids (e.g., triamcinolone, anecortave acetate) or intravitreal or peribulbar steroid in the study eye within past 3 months.
10. Concurrent use of systemic anti-VEGF agents.
11. History of vitrectomy, submacular surgery or other surgical intervention for AMD, corneal transplant or any device implantation in the study eye.
12. Intraocular surgery (including cataract surgery) in the study eye within 2 months prior to randomization.
13. Concurrent treatment with an investigational drug or device in the non-study eye.
14. Previous participation in any studies of investigational drugs within 30 days or as prescribed in that study (whichever is later) preceding the initial study treatment.

Other Ocular Conditions:

15. CNV in the study eye due to causes other than AMD such as histoplasmosis, trauma, or pathological myopia etc. or CNV lesion not likely to respond to ranibizumab.
16. Active or ongoing ocular infection (e.g. infectious conjunctivitis, keratitis, scleritis, or endophthalmitis) or severe inflammation in either of the eyes.
17. Any concurrent intraocular condition in the study eye that could either require medical or surgical intervention during the 3-month study period or that could contribute to a loss (of at least 2 Snellen equivalent lines) of best corrected visual acuity over the 3-months study period (e.g. diabetic retinopathy, progressive retinal disease or retinal pathology, cataract, glaucoma, uveitis, previous corneal transplant, the refractive error more than -8 diopters of myopia etc.). The decision regarding exclusion was to be based on the opinion of the investigator.

In study LRP/LUBT010/2022/001 subjects were excluded from the study if they met any of the following criteria:

1. Known hypersensitivity to ranibizumab or any of the components of study medication.
2. Known history of allergy to fluorescein dye.
3. Patients with coexisting CNV lesions secondary to AMD in the non-study eye that would require simultaneous treatment with anti-VEGF therapies during the study period.
4. Scar, fibrosis, or atrophy involving the center of the fovea in the study eye as assessed by fluorescein angiography (FA).
5. History of vitrectomy, submacular surgery, or other surgical intervention for AMD in the study eye.
6. Any other pathology involving the CNV lesion like retrofoveolar atrophy or permanent structural damage to fovea.

7. Vitreous hemorrhage or history of rhegmatogenous retinal detachment, retinal pigment epithelial tears or rips involving the macula or macular hole (stage 1 to 4) in the study eye as assessed by FA.
8. Uncontrolled glaucoma as evident by progressive damage to optic nerve or visual fields despite optimum therapy; or steroid-induced glaucoma with continued use of steroids that requires intraocular pressure (IOP)-lowering treatment.
9. History of serious complications following surgery in the study eye within 1 year prior to randomization.
10. Previous treatment with intravenous anti-VEGF agents or intravitreal anti-VEGF agents such as Bevacizumab, Ranibizumab, Aflibercept, Pegaptanib, Brolucizumab in either of the eyes.
11. Previous treatment with intravitreal steroids (e.g., triamcinolone, anecortave acetate) in the study eye within 3 months prior to randomization.
12. Previous treatment with intravitreal steroid implant (like Ozurdex®) within 6 months prior to randomization.
13. Concurrent use of systemic anti-VEGF agents.
14. Intraocular surgery (including cataract surgery) in the study eye within 3 months prior to randomization.
15. Concurrent treatment with an investigational drug or device in the non-study eye.
16. Previous participation in any studies of investigational drugs within 30 days or as prescribed in that study (whichever is later) preceding the initial study treatment.
17. Patients who have diabetic macular edema (DME) and/or background or proliferative retinopathy will be excluded. Likewise, anyone with significant posterior subcapsular cataract (PSC) should be excluded.
18. CNV in the study eye due to causes other than AMD such as histoplasmosis, trauma, or pathological myopia etc. or CNV lesion not likely to respond to ranibizumab.
19. Active or ongoing ocular infection (e.g., infectious conjunctivitis, keratitis, scleritis, or endophthalmitis) or severe inflammation in either of the eyes.
20. Any concurrent intraocular condition in the study eye that could either require medical or surgical intervention during the study period or conditions that could contribute to a loss (of at least 2 Snellen equivalent lines) of BCVA over the study period (e.g., progressive retinal disease or retinal pathology, cataract, glaucoma, uveitis, previous corneal transplant, the refractive error more than -8 diopters of myopia etc.). The decision regarding exclusion is to be based on the opinion of the investigator.
21. Any patient with cloudy media from any cause that prevents adequate visualization of the fundus with indirect ophthalmoscopy should be excluded.
22. Patients with seropositivity for hepatitis B, hepatitis C, human immunodeficiency virus (HIV) antibody, or any immunodeficiency and/ or immunosuppressive disease or active systemic infection.
23. History or presence of concurrent systemic diseases or dysfunctions requiring significant medical/surgical intervention during study period that might affect interpretation of the results or contraindicates the use of ranibizumab or render the patient at high risk for treatment complications based on the Investigator's judgment such as:
    - Cardiovascular disease (e.g., stroke, myocardial infarction), uncontrolled respiratory, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic,

dermatologic, neurologic (e.g., optic neuropathy), metabolic, pulmonary, autoimmune disease or psychiatric disease based on previous history and relevant reports of clinical examination, laboratory tests, or electrocardiogram etc.

Reason for exclusion: This being biosimilar development the main objective of the studies was to compare the efficacy and safety with the reference product. The patients were excluded to have a uniform population and reduce variability.

Is it considered to be included as missing information? No.

Rationale: List of safety concerns are aligned to the reference medicinal product.

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

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

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

Table SIV.3: 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
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	
Population with relevant different ethnic origin	
Subpopulations carrying relevant genetic polymorphisms	
Pediatric Population	

Part II: Module SV - Post-authorisation experience

Part II: Module SVI - Additional Europe considerations for the safety specification

Ranibizumab does not belong to a pharmacological class associated with drug abuse. There is no known potential for misuse for illegal purposes, e.g. as a recreational drug or to facilitate assault. Although, the abuse potential of Ranibizumab was not specifically studied, there were no adverse events were reported that would suggest that Ranibizumab may lead to drug

abuse. Furthermore, this is a prescription only medicine and its administration is limited to experienced ophthalmologist which makes it unlikely to be available for misuse for illegal purposes.

Part II: Module SVII - Identified and potential risks

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

In this Risk Management Plan (RMP), safety concerns are aligned with the European Union Risk Management Plan (EU-RMP) V 22.0 of reference medicinal product Lucentis® updated on 17 May 2023, cited in December 2024[1].

Safety concerns	Name of Safety concerns
Important identified risks	• Infectious Endophthalmitis • Intraocular inflammation • Retinal detachment and Retinal tear • Intraocular pressure increase
Important potential risks	• None
Missing information	• None

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

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

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

- Headache
- Nasopharyngitis
- Urinary tract infection
- Anaemia
- Hypersensitivity
- Anxiety
- Cough
- Nausea
- Eye pain
- Ocular hyperaemia
- Vitritis
- Retinal haemorrhage
- Visual disturbance
- Vitreous floaters
- Conjunctival haemorrhage
- Eye irritation
- Foreign body sensation in eyes
- Lacrimation increased
- Blepharitis
- Dry eye

- Eye pruritus
- Visual acuity reduced
- Vitreous haemorrhage
- Vitreous disorder
- Uveitis
- Iritis
- Iridocyclitis
- Cataract
- Cataract subcapsular
- Posterior capsule opacification
- Punctuate keratitis
- Corneal abrasion
- Interior chamber flare
- Vision blurred
- Injection site haemorrhage
- Eye haemorrhage
- Conjunctivitis
- Eye discharge
- Photopsia
- Photophobia
- Ocular discomfort
- Eyelid oedema
- Eyelid pain
- Conjunctival hyperaemia
- Hypopyon
- Hyphaema
- Keratopathy
- Iris adhesion
- Corneal deposits
- Corneal oedema
- Corneal striae
- Injection site pain
- Injection site irritation
- Abnormal sensation in eye
- Eyelid irritation
- Allergic reactions (rash, urticaria, pruritus, erythema)
- Arthralgia

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

Known risks that require no further characterisation and are followed up via routine pharmacovigilance activities, namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers:
None.

Known risks that do not impact the risk-benefit profile:
Not Applicable.

Other reasons for considering the risks not important:
None.

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

Risks considered important for inclusion in the RMP list of safety concerns	
Important Identified Risk	
1. Infectious Endophthalmitis	Intravitreous injections, including those with Ranibizumab, have been associated with endophthalmitis. Proper aseptic injection techniques must always be used when administering Ranibizumab. The most critical factor in the causation of endophthalmitis is the breakdown of the ocular blood barrier and intraocular colonization by pathogens (bacteria/fungi). In exogenous endophthalmitis, the inciting injury or surgery causes disruption of globe integrity, which allows invasion of the pathogens[19]. Endophthalmitis is defined as an inflammation of the inner coats of the eye, resulting from intraocular colonization of infectious agents with exudation within intraocular fluids. It is a potentially blinding condition[20].
2. Intraocular inflammation	Uveitis is traditionally considered an autoimmune disease initiated by loss of immune tolerance to retinal proteins (eg, S-antigen and retinoid-binding protein, RBP-3) and tyrosinase-related products,12 and orchestrated by two subsets of CD4+ T cells that secrete their signature cytokines interferon (IFN)-γ for Th1 and interleukin (IL-17) for Th17 cells[21]. Intravitreous injections, including those with Ranibizumab, have been associated with Intraocular Inflammation. Proper aseptic injection techniques must always be used when administering Ranibizumab. Ranibizumab is contraindicated in patients with active severe intraocular inflammation. Patients should also be instructed to report if an intraocular inflammation increases in severity, which may be a clinical sign attributable to intraocular antibody formation.
3 Retinal detachment and Retinal tear	Retinal detachment leads to visual distortion, and untreated retinal detachment leads to retinal cell death and loss of vision. When initiating ranibizumab therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.

Risks considered important for inclusion in the RMP list of safety concerns	
	Intravitreous injections, including those with Ranibizumab, have been associated with Retinal detachment and Retinal tear. Proper aseptic injection techniques must always be used when administering Ranibizumab.
4 Intraocular pressure increase	In adults, transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of Ranibizumab. Sustained IOP increases have also been identified. Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately. Sudden increase of intraocular pressure can lead to intraocular micro barotrauma and cause ischemic effects and mechanical stress to retinal nerve fibre layer[22]. The mechanism by which sustained IOP elevation occurs following IVT ranibizumab treatment is unknown. Currently three mechanisms seem likely; these may act in isolation or have a combined effect. The first is microparticle obstruction, a process involving diffusion of the 48-kDa ranibizumab antibody fragment into the anterior chamber leading to physical obstruction and increased resistance within the trabecular meshwork. A similar process may occur due to the presence of silicone droplets or protein microaggregates from delivery equipment or packaging. Low-grade inflammation following injection is considered another potential cause, as it has the potential to alter fibroblast proliferation and scar deposition within the trabecular meshwork. Repeat trauma to the trabecular meshwork due to immediate and recurrent IOP spikes following injection has also been proposed[23].

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

Not applicable as this is initial RMP

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

Presentation of important identified risks and important potential risks	
Important identified risk: Infectious endophthalmitis	
MedDRA terms (Preferred Terms)	Endophthalmitis
Potential mechanism	Intravitreous injections, including those with ranibizumab, have been associated with endophthalmitis. Proper aseptic injection techniques must always be used when administering ranibizumab.

Evidence source(s) and strength of evidence	Infectious endophthalmitis can possibly lead to loss of vision and in sometimes surgical removal of eye[1].
Characterisation of the risk	In the days following Ranibizumab administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, the patient should seek immediate care from an ophthalmologist.
Risk factors and risk groups	LUBT010 is contraindicated in patients with active or suspected ocular or periocular infections or in patients with active severe intraocular inflammation.
Preventability	Proper aseptic injection techniques must always be used when administering ranibizumab. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Adult patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.
Impact on the risk-benefit balance of the product	The risk-benefit balance is anticipated to remain unchanged if the drug is used in accordance with the authorised product label. Lupin will implement routine pharmacovigilance system and activities to collect, process and report to the drug regulatory authority of Europe.
Public health impact	Public health impact of the risk is anticipated to be minimal if the drug is used in accordance with the authorised product label. Lupin will implement the routine pharmacovigilance system and activities to monitor the safety profile of the product.
Important identified risk: Intraocular Inflammation	
MedDRA terms (Preferred Terms)	Eye Inflammation
Potential mechanism	Inflammation associated with intravitreal anti-VEGF injection manifests with a broad range of clinical features which may be generally categorized into two mechanisms. The first mechanism results in an acute onset sterile inflammation. This type of inflammation occurs on a spectrum, ranging from subclinical anterior chamber inflammation to significant inflammation mimicking endophthalmitis. The second mechanism is a delayed onset inflammatory vasculitis which has been described with brolucizumab. The overall inflammatory rates vary between specific anti-VEGF agents and a variety of outside factors may influence observed rates of inflammation[25].
Evidence source(s) and strength of evidence	Intraocular inflammation can possibly lead to a loss of visionand in sometimes surgical removal of eye[1]
Characterisation of the risk	United States physician-level claims data covering an 18-month period for each therapy were analyzed. The primary analysis compared severe ocular inflammation event rates per 1000 injections. Sensitivity and subgroup analyses evaluated the impact of factors including intraocular surgery, intravitreal

	antibiotic administration, and previous intravitreal injections. The analysis included 432,794 injection claims (ranibizumab *n* = 253,647, aflibercept *n* = 179,147); significantly, more unique severe ocular inflammation events occurred in patients receiving aflibercept than ranibizumab (1.06/1000 injections, 95% confidence interval [CI], 0.91–1.21, vs. 0.64/1000 injections, 95% CI 0.54–0.74; $p < 0.0001$). Comparable results were observed for analyses of patients who had undergone glaucoma or cataract surgeries, had antibiotic-associated endophthalmitis, had non-antibiotic-associated endophthalmitis, and were non-treatment-naive. In contrast, no significant differences in severe ocular inflammation claims were recorded in treatment-naive patients who had no record of anti-VEGF treatment in the 6 months preceding the index claim. No significant change occurred in the rate of severe ocular inflammation claims over time following ranibizumab treatment[26].
Risk factors and risk groups	Proper aseptic injection techniques must always be used when administering ranibizumab.
Preventability	Proper aseptic injection techniques must always be used when administering ranibizumab. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Adult patients should be instructed to report any symptoms suggestive of an intraocular inflammation without delay. Patients should also be instructed to report if an intraocular inflammation increases in severity, which may be a clinical sign attributable to intraocular antibody formation.
Impact on the risk-benefit balance of the product	The risk-benefit balance is anticipated to remain unchanged if the drug is used in accordance with the authorised product label. Lupin will implement the routine pharmacovigilance system and activities to collect, process and report to the drug regulatory authority of Europe.
Public health impact	Public health impact of the risk is anticipated to be minimal if the drug is used in accordance with the authorised product label. Lupin will implement the routine pharmacovigilance system and activities to monitor the safety profile of the product.
Important identified risk: Retinal detachment and Retinal tear	
MedDRA terms (Preferred Terms)	Retinal detachment, Retinal tear

Potential mechanism	Rhegmatogenous retinal detachment occurs when the liquefied vitreous enters between the choroid and the pigmented epithelium detaching the retinal layer from the underlying choroid. Traction retinal detachment occurs when scar tissue or other abnormal tissue grows on the surface of the retina, pulling the retina away from the layer beneath it. This does not necessarily cause a specific tear or break in the retina. In patients with advanced stages of ROP, retinal detachment develops when neovascularization progresses and proliferous fibrous and vascular tissue lead to traction at the demarcation zone between vascular and avascular retina often thickened into an ophthalmoscopically visible ridge. Exudative retinal detachment occurs when blood or fluid from the choroid flows into the space under the retina and separates the retina from the layer beneath it. The detachment does not involve tears in the retina or traction from the vitreous. Exudative retinal detachment is most often a complication of other diseases including macular degeneration, eye tumors, inflammation in the choroid or the retina, or severe high blood pressure
Evidence source(s) and strength of evidence	Retinal detachment leads to visual distortion, and untreated retinal detachment leads to retinal cell death and loss of vision[1]. Less frequently reported, but more serious, adverse reactions include retinal detachment, retinal tear.
Characterisation of the risk	This risk needs to be characterised further based on data available from pharmacovigilance activities.
Risk factors and risk groups	The following conditions might increase the risk for retinal detachment: previous retinal detachment or retinal tear, eye tumors, inflammation in the choroid or the retina, eye injury, high myopia or severe high blood pressure[1].
Preventability	In most cases a retinal detachment or retinal tear cannot be prevented.. Treatment should be discontinued in subjects with rhegmatogenous retinal detachment or stage 3 or 4 macular holes.
Impact on the risk-benefit balance of the product	The risk-benefit balance is anticipated to remain unchanged if the drug is used in accordance with the authorised product label. Lupin will implement the routine pharmacovigilance system and activities to collect, process and report to the drug regulatory authority of Europe.

Public health impact	Public health impact of the risk is anticipated to be minimal if the drug is used in accordance with the authorised product label. Lupin will implement the routine pharmacovigilance system and activities to monitor the safety profile of the product.
Important identified risk: Intraocular Pressure Increase	
MedDRA terms (Preferred Terms)	Glaucoma
Potential mechanism	The injected volume of ranibizumab may lead to an increase in IOP.
Evidence source(s) and strength of evidence	In adults, transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of ranibizumab. Sustained IOP increases have also been identified. Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately.
Characterisation of the risk	Elevated IOP occurred at a significantly higher rate in eyes receiving IVT ranibizumab (7.47%; n = 9) compared with control (0.93%; n = 1). Patients with preexisting glaucoma or ocular hypertension (OHT) were more likely to develop elevated IOP after IVT ranibizumab injection[23].
Risk factors and risk groups	Pre-existing high IOP; ranibizumab should not be administered in the event of an intraocular pressure of 30 mmHg[1].
Preventability	Adult patients are advised to call their ophthalmologist if they have eye pain or vision loss or other signs or symptoms that may indicate acute increase of IOP following an injection.
Impact on the risk-benefit balance of the product	The risk-benefit balance is anticipated to remain unchanged if the drug is used in accordance with the authorised product label. Lupin will implement the routine pharmacovigilance system and activities to collect, process and report to the drug regulatory authority of Europe.
Public health impact	Public health impact of the risk is anticipated to be minimal if the drug is used in accordance with the authorised product label. Lupin will implement the routine pharmacovigilance system and activities to monitor the safety profile of the product.

Part II: Module SVII 3.2- Presentation of missing information

Not applicable

Part II: Module SVIII- Summary of the safety concerns

In this Risk Management Plan (RMP), safety concerns are aligned with the European Union Risk Management Plan (EU-RMP) V 22.0 of reference medicinal product Lucentis® updated on 17 May 2023, cited in December 2024.

Table SVIII.1: Summary of safety concerns

Summary of Safety concerns	
Important identified risks	• Infectious Endophthalmitis • Intraocular inflammation • Retinal detachment and Retinal tear • Intraocular pressure increase
Important potential risks	• None
Missing information	• None

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

III.1 Routine pharmacovigilance activities

In addition to routine pharmacovigilance activities, specific adverse reaction follow-up questionnaires are in place to further characterise the risk of Ranibizumab.

Specific adverse reaction follow-up questionnaires will be used to collect further data to help further characterize and/or closely monitor each of the respective safety concern specified below:

- Infectious endophthalmitis

The Specific adverse reaction follow-up questionnaires are provided in Annex 4.

III.2 Additional pharmacovigilance activities

None.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

Part IV: Plan for post-authorization efficacy studies

There are no ongoing or proposed post-authorisation efficacy studies for Ranluspec®.

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

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

Safety concern	Routine risk minimisation activities
Important identified risks	
1. Infectious endophthalmitis	**<u>Routine risk communication:</u>** <u>SmPC:</u> Section 4.2 “Posology and method of administration” section 4.3 “Contraindications”, Section 4.4 “Special Warnings and Precautions” Section 4.8 “Undesirable effects” Section 6.6 “Special precautions for disposal and other handling PL: Section 4 “Possible side effects” **<u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u>** <u>SmPC:</u> • Section 4.2 “Posology and method of administration” includes recommendation that LUBT010 must be administered by a qualified ophthalmologist experienced in intravitreal injections. • As per section 4.3 “Contraindications”, this product is contraindicated in with active or suspected ocular or periocular infections and in patients with active severe intraocular inflammation. • Section 4.4 “Special Warnings and Precautions” states that, Intravitreous injections, including those with ranibizumab, have been associated with endophthalmitis. Proper aseptic injection techniques must always be used when administering ranibizumab. In addition, patients should be

Safety concern	Routine risk minimisation activities
	monitored during the week following the injection to permit early treatment if an infection occurs. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay. • Section 6.6 “Special precautions for disposal and other handling” include guidance on how to administer intravitreal injection and prevention of this event. PL: • Section 4 “Possible side effects” of patient leaflet informs patients to tell the doctor immediately if there are symptoms like eye pain or worsening of eye redness. **Other routine risk minimization measures beyond the Product Information:** **Pack size:** For vial: One vial (type I glass) containing 0.23 ml sterile solution. For PFS: one pre-filled syringe. **Legal status:** Prescription only medicine
2. Intraocular Inflammation	**Routine risk communication:** SmPC: Section 4.3 “Contraindications” Section 4.4 “Special Warnings and Precautions” PL: Section 2 “What you need to know before you are given LUBT010” Section 4 “Possible side effects” **Routine risk minimisation activities recommending specific clinical measures to address the risk:**

Safety concern	Routine risk minimisation activities
	SmPC: • Section 4.3 “Contraindications” states that, Ranibizumab is contraindicated in patients with active severe intraocular inflammation • Section 4.4 “Special Warnings and Precautions” states that, o Intravitreous injections, including those with ranibizumab, have been associated with intraocular inflammation. Proper aseptic injection techniques must always be used when administering ranibizumab. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Patients should be instructed to report any symptoms suggestive of intraocular inflammation, without delay. o Patients should also be instructed to report if an intraocular inflammation increases in severity, which may be a clinical sign attributable to intraocular antibody formation. PL: • Section 2 “What you need to know before you are given LUBT010” mentions that, o You must not receive LUBT010, if you have pain or redness (severe intraocular inflammation) in your eye. o Subsection of warnings and precautions mentions that, it is important to identify and treat such an infection or retinal detachment as soon as possible. Please tell your doctor immediately if you develop signs such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in your vision or increased sensitivity to light. In some patients the eye pressure may increase for a short period directly after the injection. This is something you may not

Safety concern	Routine risk minimisation activities
	notice; therefore, your doctor may monitor this after each injection. **<u>Other routine risk minimization measures beyond the Product Information</u>:** **Pack size:** For vial: One vial (type I glass) containing 0.23 ml sterile solution. For PFS: one pre-filled syringe. **Legal status**: Prescription only medicine
3. Retinal Detachment and retinal tear	**<u>Routine risk communication</u>**: **<u>SmPC:</u>** Section 4.4 “Special Warnings and Precautions” Section 4.8 “Undesirable effects” **PL:** Section 2 “What you need to know before you are given LUBT010” Section 4 “Possible side effects” **<u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u>** **<u>SmPC:</u>** • Section 4.4 “Special Warnings and Precautions” states that, Intravitreous injections, including those with ranibizumab, have been associated with retinal detachment and retinal tear. Proper aseptic injection techniques must always be used when administering ranibizumab. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. This section also states that the dose should be withheld, and treatment should not be resumed earlier than the next scheduled

Safety concern	Routine risk minimisation activities
	treatment in the event of a retinal break, when initiating ranibizumab therapy, caution should be used in patients with the risk factors for retinal pigment epithelial tears. Treatment should be discontinued in subjects with rhegmatogenous retinal detachment or stage 3 or 4 macular holes. **PL:** • Section 2 “What you need to know before you are given LUBT010” mentions that, talk to your doctor before you are given LUBT010. It is important to identify and treat an infection or retinal detachment as soon as possible. Please tell your doctor immediately if you develop signs such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in your vision or increased sensitivity to light. It is important to identify and treat serious side effects such as infection of the eyeball or retinal detachment as soon as possible. **Other routine risk minimization measures beyond the Product Information:** **Pack size:** For vial: One vial (type I glass) containing 0.23 ml sterile solution. For PFS: one pre-filled syringe. **Legal status:** Prescription only medicine
4. Intraocular pressure increase	**Routine risk communication:** **SmPC:** Section 4.4 “Special Warnings and Precautions” Section 4.8 “Undesirable effects” Section 4.9 “Overdose” Section 5.3 “Preclinical safety data” **PL:**

Safety concern	Routine risk minimisation activities
	Section 2 “What you need to know before you are given LUBT010” 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” states that, in adults, transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of ranibizumab. Sustained IOP increases have also been identified. Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately. Patients should be informed of the symptoms of these potential adverse reactions and instructed to inform their physician if they develop signs such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in their vision, or increased sensitivity to light. It also mentions that the dose should be withheld, and treatment should not be resumed earlier than the next scheduled treatment in the event of an intraocular pressure of ≥30 mmHg; • Section 4.9 “overdose” states that if an overdose occurs, intraocular pressure should be monitored and treated, if deemed necessary by the attending physician. **PL:** • Section 2 “What you need to know before you are given LUBT010” mentions that, please tell your doctor immediately if you develop signs such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in your vision or increased sensitivity to light..

Safety concern	Routine risk minimisation activities
	<u>Other routine risk minimization measures beyond the Product Information</u>: **Pack size:** For vial: One vial (type I glass) containing 0.23 ml sterile solution. For PFS: one pre-filled syringe. Legal **status**: Prescription only medicine
Important potential risks: None	
Missing Information: None	

V.2. Additional Risk Minimisation Measures

Additional risk minimisation measures (aRMM) are in place for important identified risks of "Infectious Endophthalmitis, Intraocular Inflammation, Retinal detachment and Retinal tear and Intraocular pressure increase".

Education material for adult patients consists of the patient information booklet (also available in spoken form in audio format).

Educational program for adult patients:

Objectives:	To ensure that patients are adequately informed about the potential to develop intraocular pressure increase, intraocular inflammation, retinal detachment and retinal tear and infectious endophthalmitis after an intravitreal injection of ranibizumab, an educational/safety advice tools for patient (information booklet) was developed.

Rationale for the additional risk minimisation activity:	The patient information booklets aim to provide adequate patient education on key signs and symptoms of potential adverse reactions and when to seek urgent attention from their physician, ensuring rapid identification and treatment of these events. Key signs and symptoms of the following identified risks are covered in the patient information booklet: *Infectious Endophthalmitis* • Infectious endophthalmitis is a serious ocular condition, often caused by an intraocular infection, and can potentially lead to blindness. • Patients need to contact their clinic immediately if they develop signs such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in their vision or increased sensitivity to light. *Intraocular Inflammation* • Intraocular inflammation can cause eye pain, worsening eye redness, blurred vision, an increased number of small particles in the patient's vision or increased sensitivity to light. *Retinal detachment and retinal tear* • Warning signs may include symptoms such as increased eye discomfort, light flashes and blurred or decreased vision. *Intraocular pressure increase* • Increases in intraocular pressure (IOP) within 60 minutes of injection of ranibizumab are very common. They may be asymptomatic, or could cause eye pain and decreased vision. In addition, the booklet contains follow-up recommendations for adequate care after the injection, including recommendations to contact the physician in case of additional questions.
Target audience and planned distribution path:	**Target audience:** patients (who are prescribed Ranibizumab) **Planned distribution path:** The booklets are made available to the patient after ranibizumab is prescribed to them as per communication plan agreed with NCA in each member state. Similarly, Patient information booklets covering the proliferative diabetic retinopathy (PDR) indication will be provided.
Plans to evaluate the effectiveness of the interventions	Process indicators and outcome indicators will be evaluated during the effectiveness check of the aRMM.

and criteria for success:	

V.3. Summary of risk minimisation measures

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
1. Infectious endophthalmitis	**Routine risk minimisation measures:** **SmPC Sections:** Section 4.2 "Posology and method of administration" Section 4.3 "Contraindications", Section 4.4 "Special Warnings and Precautions" Section 4.8 "Undesirable effects" Section 6.6 "Special precautions for disposal and other handling" **PL Sections:** Section 4 "Possible side effects" **Pack size:** For vial: One vial (type I glass) containing 0.23 ml sterile solution. For PFS: one pre-filled syringe. **Legal status**: prescription only medicine **Additional risk minimisation measure:** Educational program for adult patients	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaires for Endophthalmitis **Additional pharmacovigilance activities:** None
2. Intraocular Inflammation	**Routine risk minimisation measures:** **SmPC Sections:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Section 4.3 "Contraindications" Section 4.4 "Special Warnings and Precautions" **PL Sections:** Section 2 "What you need to know before you are given LUBT010" Section 4 "Possible side effects" **Pack size:** For vial: One vial (type I glass) containing 0.23 ml sterile solution. For PFS: one pre-filled syringe. **Legal status**: prescription only medicine **Additional risk minimisation measure:** Educational program for adult patients	**Additional pharmacovigilance activities:** None
3. Retinal Detachment and retinal tear	**Routine risk minimisation measures:** **SmPC Sections:** Section 4.4 "Special Warnings and Precautions" Section 4.8 "Undesirable effects" **PL Sections:** Section 2 "What you need to know before you are given LUBT010" Section 4 "Possible side effects" **Pack size:** For vial: One vial (type I glass) containing 0.23 ml sterile solution.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	For PFS: one pre-filled syringe. **Legal status**: prescription only medicine **Additional risk minimisation measure:** Educational program for adult patients	
4. Intraocular pressure increase	**Routine risk minimisation measures:** **SmPC Sections:** Section 4.4 “Special Warnings and Precautions” Section 4.8 “Undesirable effects” Section 4.9 “Overdose” Section 5.3 “Preclinical safety data” **PL Sections:** Section 2 “What you need to know before you are given LUBT010” Section 4 “Possible side effects” **Pack size:** For vial: One vial (type I glass) containing 0.23 ml sterile solution. For PFS: one pre-filled syringe. **Legal status**: prescription only medicine **Additional risk minimisation measure:** Educational program for adult patients	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Part VI: Summary of the risk management plan

Summary of risk management plan for Ranluspec® 10 mg/mL solution for intravitreal injection in vial and prefilled syringe (Ranibizumab)

This is a summary of the Risk Management Plan (RMP) for Ranluspec® 10 mg/mL solution for intravitreal injection in vial and prefilled syringe. The RMP details important risks of Ranluspec® 10 mg/mL solution for intravitreal injection in vial and prefilled syringe, how these risks can be minimised, and how more information will be obtained about Ranluspec® 10 mg/mL solution for intravitreal injection in vial and prefilled syringe`s risks and uncertainties (missing information).

Ranluspec® 10 mg/mL solution for intravitreal injection in vial and prefilled syringe Package Leaflet`s Summary of product Characteristics (SmPC) and Package leaflet (PL) give essential information to healthcare professionals and patients on how Ranluspec® 10 mg/mL solution for intravitreal injection in vial and prefilled syringe should be used.

I. The medicine and what it is used for

In adults, Ranibizumab is indicated for

- The treatment of neovascular (wet) age-related macular degeneration (AMD)
- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of proliferative diabetic retinopathy (PDR)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- The treatment of visual impairment due to choroidal neovascularisation (CNV)

It contains Ranibizumab as the active substances and it is given as an intravitreal injection.

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

Important risks of Ranluspec® 10 mg/mL solution for intravitreal injection in vial and prefilled syringe, together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for Ranluspec® 10 mg/mL solution for intravitreal injection in vial and prefilled syringe are:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL addressed to patients and healthcare professionals;

- Important advice on the medicine’s packaging; and and how to use Ranluspec® 10 mg/mL solution for intravitreal injection in vial and prefilled syringe

- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.

- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In case of Ranluspec® 10 mg/mL solution for intravitreal injection in vial and prefilled syringe, these measures are supplemented by *additional risk minimisation measures* mentioned under relevant important risks below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, 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 Ranluspec® 10 mg/mL solution for intravitreal injection in vial and prefilled syringe is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Ranluspec® 10 mg/mL solution for intravitreal injection in vial and prefilled syringe are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Ranluspec® 10 mg/mL solution for intravitreal injection in vial and prefilled syringe. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Infectious endophthalmitis • Intraocular Inflammation • Retinal Detachment and retinal tear • Intraocular pressure increase
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

Important identified risks: Infectious endophthalmitis	
Evidence for linking the risk to the medicine	Intravitreous injections, including ranibizumab have been associated with endophthalmitis. Infectious endophthalmitis can possibly lead to a loss of vision and in sometimes surgical removal of eye.
Risk factors and risk groups	LUBT010 is contraindicated in patients with active or suspected ocular or periocular infections or in patients with active severe intraocular inflammation.
Risk minimisation measures	Routine risk minimisation measures: <u>SmPC sections:</u> Section 4.2 “Posology and method of administration” section 4.3 “Contraindications”, Section 4.4 “Special Warnings and Precautions” Section 4.8 “Undesirable effects” Section 6.6 “Special precautions for disposal and other handling PL sections: Section 4 “Possible side effects” Additional risk minimisation measures: Educational program for adult patients
Important identified risks: Intraocular Inflammation	
Evidence for linking the risk to the medicine	Intravitreous injections, including ranibizumab have been associated with intraocular inflammation. Intraocular inflammation can possibly lead to a loss of vision and in sometimes surgical removal of eye.
Risk factors and risk groups	Proper aseptic injection techniques must always be used when administering ranibizumab.
Risk minimisation measures	Routine risk minimisation measures: <u>SmPC sections:</u> Section 4.3 “Contraindications” Section 4.4 “Special Warnings and Precautions” PL sections: Section 2 “What you need to know before you are given LUBT010 Section 4 “Possible side effects” Additional risk minimisation measures: Educational program for adult patients

Important identified risks: Retinal detachment and Retinal tear	
Evidence for linking the risk to the medicine	Retinal detachment leads to visual distortion, and untreated retinal detachment leads to retinal cell death and loss of vision[1]. Less frequently reported, but more serious, adverse reactions include retinal detachment, retinal tear.
Risk factors and risk groups	The following conditions might increase the risk for retinal detachment: previous retinal detachment or retinal tear, eye tumors, inflammation in the choroid or the retina, eye injury, high myopia or severe high blood pressure[1].
Risk minimisation measures	Routine risk minimisation measures: <u>SmPC sections:</u> Section 4.4 “Special Warnings and Precautions” Section 4.8 “Undesirable effects” PL sections: Section 2 “What you need to know before you are given LUBT010” Section 4 “Possible side effects” Additional risk minimisation measures: Educational program for adult patients
Important identified risks: Intraocular Pressure Increase	
Evidence for linking the risk to the medicine	In adults, transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of ranibizumab. Sustained IOP increases have also been identified. Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately.
Risk factors and risk groups	Pre-existing high IOP; ranibizumab should not be administered in the event of an intraocular pressure of 30 mmHg.
Risk minimisation measures	Routine risk minimisation measures: <u>SmPC sections:</u> Section 4.4 “Special Warnings and Precautions” Section 4.8 “Undesirable effects” Section 4.9 “Overdose” Section 5.3 “Preclinical safety data” <u>PL sections</u>: Section 2 “What you need to know before you are given LUBT010”

	Section 4 “Possible side effects” Additional risk minimisation measures: Educational program for adult patients

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 Ranluspec® 10 mg/mL solution for intravitreal injection in vial and prefilled syringe.

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

There are no studies required of Ranluspec® 10 mg/mL solution for intravitreal injection in vial and prefilled syringe.

Part VII: Annexes

Annex 1- EudraVigilance Interface

Not applicable

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

Not applicable.

Annex 3- Protocol for proposed, on-going and completed studies in the Pharmacovigilance plan

Not applicable.

Annex 4- Specific adverse drug reaction follow-up forms

Annex 4a Specific adverse drug reaction follow up form for Endophthalmitis

In addition to collecting routine information for this AE, please ensure the following additional information is provided and/or confirmed.

Event Description:

- Date of last ranibizumab injection before event onset:
- Number of Ranibizumab injections received before event onset:
- Eye(s) affected: ☐Right eye ☐Left eye ☐Both eyes
- Was the event in the injected eye? ☐Yes ☐No ☐Unknown
- Did the patient have eye pain as a presenting symptom? ☐Yes ☐No ☐Unknown
- Did the patient have any other presenting symptom(s)? ☐Yes ☐No ☐Unknown
  - If yes, please describe_____
- Did the patient receive prophylactic topical antibiotics prior to injection?

  ☐Yes ☐No ☐Unknown
  - If yes, for how many days?_____
- Did patient receive post injection antibiotics? ☐Yes ☐No ☐Unknown
  - If yes, for how many days?_____
- Was full aseptic technique used when injection was administered? (e.g. use of sterile gloves, drape, eye speculum, povidone iodine flush)

  ☐Yes ☐No ☐Unknown
  - If no, please describe what was used_____
- Was a culture done?

  ☐Yes ☐No ☐Unknown
  - If yes, what were the results?_____
- Any other relevant examination or laboratory data?_____
- Any other relevant information?_____

Relevant medical history (concurrent and pre-existing conditions):

- Did the patient receive prior laser therapy?

  ☐Yes ☐No ☐Unknown

- If yes, please provide date and which eye(s) was treated_____

- Any medications administered via intravitreal injection previous to AE?

  ☐Yes ☐No ☐Unknown

  - If yes, please describe, including which eye(s) was treated_____

- Prior history of endophthalmitis? ☐Yes ☐No ☐Unknown

  - If yes, please describe including date of occurrence and affected eye_____

Prior history of periocular infection? ☐Yes ☐No ☐Unknown

- If yes, please describe including date of occurrence, affected eye, therapeutic management, and outcome (ongoing or resolved)
  _____

- Prior eye surgery or trauma to affected eye(s)? ☐Yes ☐No ☐Unknown
  - If yes, please describe including date of occurrence and affected eye_____

- 1s the patient immunocompromised? ☐Yes ☐No ☐Unknown
  - If yes, please describe_____

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)

The Marketing Authorisation Holder (MAH) shall ensure that, following discussions and agreements with National Competent Authorities (NCA) in each member state where Ranluspec is marketed, at launch and after launch all ophthalmological clinics where Ranluspec is expected to be used for treatment of adult patients are provided with an up-to-date patient information booklet (including audio format).

Key messages of the additional risk minimization measures for adult patients in the indications of nAMD, CNV, DME, RVO and PDR

The patient booklet

The patient educational material will be developed and will be made available as per communication plan agreed with NCA in each member state, in order to support the safe use of ranibizumab. The patient booklet provides information on the key signs and symptoms of potential adverse reactions, ensuring rapid identification and treatment of these events.

The patient information pack should be provided in both the form of patient booklet and in audio format that will contain following key elements:

- Patient information leaflet
- How to prepare for Ranluspec treatment
- What are the steps following treatment with Ranluspec
- Key signs and symptoms of serious adverse events including increased intraocular pressure, intraocular inflammation, retinal detachment and retinal tear and infectious endophthalmitis
- When to seek urgent attention from the health care provider

Details of proposed educational program for adult patients

To ensure that patients are adequately informed about potential adverse events of ranibizumab, a patient information booklet will be made available.
The booklets aim to provide adequate patient education on:

- What is nAMD, CNV (including secondary to pathologic myopia), PDR with or without DME, and RVO
- How does ranibizumab work, what to expect from ranibizumab treatment, and how is ranibizumab administered
- What are the key signs and symptoms of serious adverse events including increased intraocular pressure, intraocular inflammation, retinal detachment and retinal tear and infectious endophthalmitis

- When to seek urgent attention from the health care provider

Key safety messages are focused on facilitating the patient recognizing the key signs and symptoms of potential adverse reactions to ensure the patient informs their ophthalmologist of these potentially severe outcomes. The following are the key safety messages to be communicated to allow early diagnosis and appropriate treatment of these events:

- It is important that patients monitor any changes in the condition of their eye and their overall wellbeing in the week following injection with ranibizumab
- Patients need to contact their clinic immediately if they develop signs such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in their vision, or increased sensitivity to light

In addition, the booklet contains follow-up recommendations for adequate care after the injection, including recommendations to contact the physician in case of additional questions.