EU Risk Management Plan

for

Rexatilux

(Ranibizumab)

RMP version to be assessed as part of this application:

RMP Version number	1.0
Data lock point for this RMP	26-Feb-2026
Date of final sign off	22-Apr-2026

Rationale for submitting an updated RMP: This Risk Management Plan (RMP) has been updated as per the CHMP day 180 List of Outstanding Issues, dated 26-Feb-2026 for Rexatilux.

Summary of significant changes in this RMP: Significant changes have been done in the following section of this RMP: Part III, and Part VII (Annex 7 and Annex 8).

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP: Not applicable

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AMD	Age-related macular degeneration
BRVO	Branch retinal vein occlusion
CNV	Choroidal neovascularisation
DME	Diabetic macular oedema
EPAR	European Public Assessment Report
EU	European Union
IOP	Intraocular pressure
PDR	Proliferative Diabetic Retinopathy
PL	Patient Leaflet
RMP	Risk Management Plan
RPE	Retinal pigment epithelial
RVO	Retinal vein occlusion
SmPC	Summary of Product Characteristics

Part I: Product(s) Overview

Table 1: Product(s) Overview

Active substance [International non-proprietary name (INN) or common name]	Ranibizumab
Pharmacotherapeutic group(s) (ATC Code)	**Pharmacotherapeutic group(s):** Ophthalmologicals, anti-neovascularisation agents **ATC code:** S01LA04
Marketing Authorisation Applicant	Intas Third Party Sales 2005, S.L.
Medicinal products to which this RMP refers	02
Invented name(s) in the European Economic Area (EEA)	Rexatilux 10 mg/ml solution for injection Rexatilux 10 mg/ml solution for injection in pre-filled syringe
Marketing authorisation procedure	Centralised Procedure (H0006634)
Brief description of the product	**Chemical class**: Ranibizumab is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment directed against human vascular endothelial growth factor A (VEGF-A), which is a glycoprotein implicated in the pathophysiology of age-related macular degeneration.
	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. $VEGF_{110}$, $VEGF_{121}$

	and $VEGF_{165}$), 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 CNV or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to RVO in adults.
	<u>Important information about its composition:</u> *Rexatilux 10 mg/ml solution for injection* One ml contains 10 mg ranibizumab*. 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 *Rexatilux 10 mg/ml solution for injection in pre-filled syringe* One ml contains 10 mg ranibizumab*. One pre-filled syringe contains 0.165 ml, equivalent to 1.65 mg ranibizumab. The extractable volume of one pre-filled syringe is 0.1 ml. This provides a usable amount to deliver a single dose of 0.05 ml containing 0.5 mg ranibizumab. *Ranibizumab is a humanised monoclonal antibody fragment produced in Escherichia coli cells by recombinant DNA technology.
Hyperlink to the Product Information	Refer to Module 1.3.1 for SmPC and PIL.
Indication(s) in the EEA	*Current* Rexatilux is indicated in adults 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)
Dosage in the EEA	*Current* **Posology:** *Adults* The recommended dose for Rexatilux 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, in the physician's opinion, visual and anatomic parameters indicate that the patient is not benefiting from continued treatment, ranibizumab should be discontinued.

	Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography). 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 BRVO* There is some experience of ranibizumab administered concomitantly with laser photocoagulation. When given on the same day, Rexatilux should be administered at least 30 minutes after laser photocoagulation. Rexatilux can be administered in patients who have received previous laser photocoagulation.

	<u>Method of administration:</u> Single-use vial/pre-filled syringe for intravitreal use only.
Pharmaceutical form(s) and strengths	*Current* **Pharmaceutical form(s):** Solution for injection **Strengths:** 10 mg/ml
Is the product subject to additional monitoring in the EU?	Yes

Part II: Safety specification

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

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

Age-related macular degeneration is the leading cause of irreversible blindness in adults over 50 years old. Genetic, epidemiological, and molecular studies are beginning to unravel the intricate mechanisms underlying this complex disease, which implicate the lipid-cholesterol pathway in the pathophysiology of disease development and progression. AMD is a neurodegenerative disease that preferentially affects the macular (central) region of the retina, although the reason for this is not clearly understood. The disease is categorized into early, intermediate, or advanced stages based on the severity of symptoms, including the number and size of drusen accompanied by hyper- or hypopigmentary changes and the presence or absence of CNV.

The term "wet AMD" refers to the advanced neovascular (or exudative) stage of the disease, which presents a more rapid loss of vision relative to geographic atrophy. Neovascular AMD arises from the growth of abnormal blood vessels from the choroid into the normally avascular sub-retinal pigment epithelium and sub-retinal regions (CNV). Although neovascular AMD represents a small proportion of total AMD cases, it accounts for the majority of blindness associated with AMD. The prevalence of AMD varies greatly by ethnicity with non-Hispanic White Europeans having the greatest disease burden. Recent study calculated pooled prevalence of ethnically diverse population-based studies of AMD (age range of 45–85 years) and confirmed that prevalence was greatest among those individuals of European descent at 12.3–30% with increasing age. Disease burden, although slightly less, is still great amongst Hispanics (10.4%), Africans (7.5%) and Asians (7.4%). Still, others have estimated a lower disease burden within the U.S., with non-Hispanic White Europeans having the highest at almost 7.3% and African-Americans at 2.4%. Regardless, it is clear that the prevalence of AMD varies by ethnicity and racial group, and therefore the role of genetic variants, environmental exposures, and their interplay in AMD susceptibility will likely vary by ethnicity as well.

[1] Pennington KL, DeAngelis MM. Epidemiology of age-related macular degeneration (AMD): associations with cardiovascular disease phenotypes and lipid factors. Eye Vis (Lond). 2016 Dec 22;3:34.

Diabetic Macular Edema (DME)[2]

Approximately 347 million persons worldwide have diabetes mellitus. The Centers for Disease Control and Prevention estimates that, in 2010, 25.8 million persons (8.3% of the United States population) had diabetes mellitus. Substantial racial/ethnic differences in the prevalence of diabetes in the United States have also been noted. National estimates report that, in persons aged 20 years and older in the Unites States, 14.2% of American Indians and Alaskan natives, 12.6% of non-Hispanic blacks, 11.8% of Hispanics, 8.4% of Asian Americans, and 7.1% of non-Hispanic whites have been diagnosed with diabetes. Diabetic eye disease is a leading cause of vision loss in persons aged 20 to 74 years. Of the visually disabling conditions in persons with diabetic eye disease, DME, left untreated, is a common cause of vision loss. Diabetic macular edema affects central vision and can lead to decline in vision ranging from slight visual blurring to blindness, substantially affecting independence and quality of life. At least since the 1980s and until 2010, focal/grid laser photocoagulation was the standard of care to treat macular edema, reduce the risk of vision loss, and increase the possibility of vision gain compared with no treatment.

Proliferative diabetic retinopathy (PDR)[3]

Proliferative diabetic retinopathy (PDR) is the most advanced stage of diabetic eye disease in both type 1 and type 2 diabetics. It occurs when the retina starts developing new blood vessels. This is referred to as neovascularization. These fragile new vessels often bleed into the vitreous and can form scar tissue. This scar tissue can lead to a tractional retinal detachment.

PDR is very serious, and can cause loss of both central and peripheral vision in patients. The prevalence of all types of diabetic retinopathy in the diabetic population increases with the duration of the disease and patient age. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) specifically is an ongoing epidemiologic study of the progression of diabetic retinopathy which has found that the 14-year rate of progression of type 1 diabetics to any retinopathy was 86 percent and the progression to proliferative diabetic retinopathy was 37 percent. Such studies underscore the importance of monitoring and control of systemic and ocular disease. The main distinguishing feature between proliferative and non-proliferative retinopathy is the presence or absence of abnormal new blood vessels. PDR is characterized by

[2] Varma R, Bressler NM, Doan QV, Gleeson M, Danese M, Bower JK, et al. Prevalence of and risk factors for diabetic macular edema in the United States. JAMA Ophthalmol. 2014 Nov;132(11):1334-1340.
[3] Chaudhary S, Zaveri J, Becker N. Proliferative diabetic retinopathy (PDR). Dis Mon. 2021 May;67(5):101140.

neovascularization of one or more of the following- iris (NVI), angle (NVA), optic disc (NVD), elsewhere in the retina (NVE), or vitreous/pre-retinal haemorrhage result from various types of neovascularization. PDR is staged as early, high-risk, or advanced.

Macular oedema secondary to retinal vein occlusion (RVO)[4]

Retinal vein occlusion is a prevalent retinal vascular disease, second only to diabetic retinopathy. Previously there was no treatment for central RVO and patients were simply observed for the development of severe complications, generally resulting in poor visual outcomes. There are two types of RVO, central RVO and branch RVO. In central RVO, there is obstruction of the major outflow channel of the eye, resulting in effects throughout the entire retina, including haemorrhages; cotton wool patches, which represent nerve layer infarcts; edema and capillary occlusion. In branch RVO, a tributary of the central retinal vein is obstructed and only the portion of the retina that is drained by the tributary is affected. The more proximal the occlusion, the greater the area of retina affected; obstruction of the superior or inferior branch of the central retinal vein affects roughly half the retina and is called a hemi RVO. The prevalence of RVO based upon several studies in the United States, Europe, Asia, and Australia is estimated to be 5.2 per 1,000. RVO accounted for 12% of eyes with visual acuity worse than 20/200. RVOs are the second most common type of retinal vascular disease, second only to diabetic retinopathy. The incidence of RVOs is estimated to be 180,000 per year in the United States and branch RVOs account for nearly 80% of those.

Visual impairment due to choroidal neovascularisation (CNV)[5]

CNV is an important sequela of a wide range of ophthalmic pathologies. The most common cause of CNV in the elderly is age-related macular degeneration, while in the young, CNV is frequently identified as secondary to high myopia, hereditary disorders, angioid streaks, and inflammation. Given the propensity of untreated CNV to result in rapid irreversible central vision loss, the importance of characterizing risk factors for CNV and prompt diagnosis is well-recognized. Indeed, central vision loss due to CNV compromises patients' ability to participate

[4] Channa R, Smith M, Campochiaro PA. Treatment of macular edema due to retinal vein occlusions. Clin Ophthalmol. 2011;5:705-713.
[5] Agarwal A., Invernizzi A., Singh R.B. et al. An update on inflammatory choroidal neovascularization: epidemiology, multimodal imaging, and management. Journal of Ophthalmic Inflammation and Infection. 2018;8:13.

in certain types of work, as well as other daily activities such as reading and driving.

Module SII - Non-clinical part of the safety specification

No non-clinical studies were performed for Intas Rexatilux 10 mg/ml solution for injection.

Module SIII - Clinical trial exposure

Clinical Study Design	Study treatment	Comment
Protocol No. 0504-19: Double Masked, Parallel Group, Randomized, Multicenter, Clinical Study to Compare Efficacy and Safety of Intas Ranibizumab with Lucentis® in Patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD)	**Test Product:** Intas Ranibizumab (biosimilar ranibizumab, Intas Pharmaceuticals Limited) **Reference Product**: Lucentis Single-use vial/PFS of 0.05 mL for intravitreal injections (ranibizumab, EU or US sourced)	Study Status – Completed Number of subjects enrolled in this study: 546

Module SIV - Populations not studied in clinical trials

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

Important Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rational (if not missing information)
Active intraocular inflammation	Standard exclusion	No	These conditions could potentially interfere

Important Exclusion criteria	**Reason for exclusion**	**Is it considered to be included as missing information?**	**Rational (if not missing information)**
Known hypersensitivity to ranibizumab or any of the components of study medication	criteria as per study protocol		with the aim/ objective of the study, or it can have impact on patient safety. The missing information has been proposed in line with reference product RMP (Lucentis - EPAR-Risk-management-plan-summary).
Any prior treatment with anti-VEGF treatment including Ranibizumab, Bevacizumab, Aflibercept and Pegaptanib (intravitreal or systemic) in either eye or intraocular use of corticosteroids in study eye.			
Any history or evidence of a concurrent intraocular condition in the study eye, including retinal diseases other than neovascular AMD, that in the judgment of the Investigator, could either require medical or surgical intervention during the course of the study to prevent or treat visual loss that might result from that condition or that limits the potential to gain visual acuity upon treatment			

Important Exclusion criteria	**Reason for exclusion**	**Is it considered to be included as missing information?**	**Rational (if not missing information)**
with the investigational product (e.g. diabetic retinopathy, cataract, uncontrolled glaucoma, uveitis, previous corneal transplant, recent cataract surgery etc.).			
Have ocular structural abnormalities that are assessed by the investigator to have a clinically significant impact on study assessments.			
Prior ocular surgery (including cataract) or any intervention in the study eye			
Presence of uncontrolled systolic blood pressure >160 mmHg or uncontrolled diastolic blood pressure >100 mmHg based on the average of 3 readings taken with the patient in a resting state (Patients with controlled blood pressure (<140/90) with stable anti-			

Important Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rational (if not missing information)
hypertensive treatment regimen will be eligible).			
History of active malignancy except for appropriately treated carcinoma in situ of the cervix, nonmelanoma skin carcinoma, and prostate cancer with a Gleason score of < 6 and a stable prostate-specific antigen for > 12 months.			
Have a history of any other neurological conditions that are assessed by the Investigator to have a significant risk of severe impact on visual function.	Standard exclusion criteria as per study protocol		

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

The clinical development programme is specific to that for biosimilars and is therefore unlikely to detect certain types of adverse reactions such as rare or uncommon 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

Type of Special Population	Exposure
Pregnant Women	Not included in the clinical development programme
Breastfeeding Women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Immunocompromised patients	Not included in the clinical development programme.
Paediatric population	Not included in the clinical development programme.
Subpopulations carrying known and relevant genetic polymorphisms	Not included in the clinical development programme

Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable

Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable- There is no potential for misuse for illegal purposes.

Module SVII - Identified and potential risks

The safety concerns of this Risk Management Plan (RMP) are considered as per EPAR-Risk-management-plan Lucentis (Ranibizumab), version 22.0, dated 12-Oct-2022, published by EMA on 17-May-2023. However, as per CHMP day 120 list of questions for Rexatilux (Ranibizumab) (EMEA/H/C/006634/0000), dated 16-Oct-2025, the important potential risk 'Neurodevelopmental impairment (ROP)' have been removed, as it is only relevant for the ROP indication. Apart from this, there is no change proposed by the MAH in safety concerns and they are mentioned in Module SVIII.

Hence this section remains "Not applicable".

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

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

Not applicable

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

Not applicable

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

Not applicable

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

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

Not applicable

SVII.3.2. Presentation of the missing information

Not Applicable

Module SVIII - Summary of the safety concerns

Table 2: 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:

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the safety concerns mentioned in "Module SVIII - Summary of the safety concerns".

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for '**Infectious endophthalmitis'**:

The MAH has proposed a targeted follow up questionnaire and is provided in Annex 4 of this RMP.

Purpose: To collect further data to help further characterize and/or closely monitor Infectious endophthalmitis.

Other forms of routine pharmacovigilance activities for 'Infectious endophthalmitis, Intraocular inflammation, Retinal detachment and retinal tear and Intraocular pressure increase':

Follow up of case reports: The minimum desired case information for ranibizumab which includes the brand name and batch number of the suspect product. Additional efforts must be made to collect this information in accordance with GVP VI.'

III.2 Additional pharmacovigilance activities:

None proposed

III.3 Summary Table of additional Pharmacovigilance activities:

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable

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

V.1 Routine Risk Minimisation Measures:

Table 3: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimization activities
Important Identified Risks	
Infectious endophthalmitis	*Routine risk communication*: • SmPC Sections 4.2, 4.3, 4.4, 4.8, 6.6. • PL Sections 2, 3, 4. *Routine risk minimisation activities recommending specific clinical measures to address the risk*: • Recommendation to minimize the potential to develop infectious endophthalmitis associated with an intravitreal injection is included in SmPC section 6.6. *Other routine risk minimisation measures beyond the Product Information*: • Pack size: one vial or one PFS for single use only. • Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections.
Intraocular inflammation	*Routine risk communication*: • SmPC Sections 4.3, 4.4. • PL Sections 2, 4. *Routine risk minimisation activities recommending specific clinical measures to address the risk*: • None.

Safety concern	Routine risk minimization activities
	Other routine risk minimisation measures beyond the Product Information: • Pack size: one vial or one PFS for one injection. • Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections.
Retinal detachment and retinal tear	*Routine risk communication*: • SmPC Sections 4.4, 4.8. • PL Sections 2, 4. *Routine risk minimisation activities recommending specific clinical measures to address the risk*: • None. *Other routine risk minimisation measures beyond the Product Information*: • Pack size: one vial or one PFS for single use only. • Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections.
Intraocular pressure increase	*Routine risk communication*: • SmPC Sections 4.4, 4.8, 4.9. • PL Sections 2, 4. *Routine risk minimisation activities recommending specific clinical measures to address the risk*: • Recommendation for monitoring and managing both intraocular pressure and the perfusion of the optic nerve head is included in SmPC section 4.4.

Safety concern	Routine risk minimization activities
	Other routine risk minimisation measures beyond the Product Information: • Pack size: one vial or one PFS for single use only. • Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections.

V.2 Additional Risk Minimisation Measures:

Additional Risk Minimisation Measures have been proposed for following risks as per the reference medicinal product.

- Infectious endophthalmitis
- Intraocular inflammation
- Retinal detachment and retinal tear
- Intraocular pressure increase.

Proposed additional risk minimisation measures are listed below and are detailed summarised in Annex 6.

Educational plan for adult patients in the indications of nAMD, CNV, DME, RVO and PDR.

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, a patient information booklet (also available in spoken form in audio-CD format) was developed. The booklets are provided to the physician for distribution to the patient after ranibizumab is prescribed to them. Similarly, Patient information booklets covering the PDR indication will be provided.

Rationale for the additional risk minimization activity:

The patient information booklets (also available in spoken form in audio-CD format) 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:

Patient information packs are prepared nationally, in line with the key important risks defined in the RMP and with each member state's national regulations and legislations. The submission of the material to the respective member state national authorities should take place before the launch of ranibizumab in a new indication (according to the national legislation in the respective countries), and the distribution of the material to all ophthalmology clinics where ranibizumab is expected to be used in adult patients.

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

Success of the proposed risk minimization measures will be evaluated by the criterion of a consistent spontaneous reporting rate of infectious endophthalmitis, intraocular inflammation, retinal detachment and retinal tear and intraocular pressure increase in adult patients at the time of the PSUR. Educational materials for adult patients have been in place since the launch of ranibizumab, and further studies to assess continued effectiveness are not considered to be required.

V.3 Summary of risk minimisation measures:

Table 4: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Infectious endophthalmitis	*Routine risk communication*: • SmPC Sections 4.2, 4.3, 4.4, 4.8, 6.6. • PL Sections 2, 3, 4. • Recommendation to minimize the potential to develop infectious endophthalmitis associated with an intravitreal injection is included in SmPC section 6.6. • Pack size: one vial or one PFS for single use only. • Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections. Additional risk minimisation measures: • Educational plan for adult patients	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up using targeted checklist. Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Intraocular inflammation	Routine risk communication: • SmPC Sections 4.3, 4.4. • PL Sections 2, 4. • Pack size: one vial or one PFS for single use only. • Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections. Additional risk minimisation measures: • Educational plan for adult patients	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Retinal detachment and retinal tear	*Routine risk communication*: • SmPC Sections 4.4, 4.8. • PL Sections 2, 4. • Pack size: one vial or one PFS for single use only. • Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: • Educational plan for adult patients	
Intraocular pressure increase	*Routine risk communication*: • SmPC Sections 4.4, 4.8, 4.9. • PL Sections 2, 4. • Recommendation for monitoring and managing both intraocular pressure and the perfusion of the optic nerve head is included in SmPC section 4.4. • Pack size: one vial or one PFS for single use only. • Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections. Additional risk minimisation measures: • Educational plan 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 Rexatilux (Rexatilux 10 mg/ml solution for injection and Rexatilux 10 mg/ml solution for injection in pre-filled syringe) (Ranibizumab)

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

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

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

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

I. The medicine and what it is used for

Rexatilux is indicated for the treatment in adult patients with:

- 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 substance, and it is given by intravitreal route.

Further information about the evaluation of Rexatilux's benefits can be found in the Rexatilux's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: European public assessment reports: background and context | European Medicines Agency (EMA)

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

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

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

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

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

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

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

II.A List of important risks and missing information

Important risks of Rexatilux are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Rexatilux. 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):

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	
Risk minimisation measures	<u>*Routine risk communication*</u>: • SmPC Sections 4.2, 4.3, 4.4, 4.8, 6.6. • PL Sections 2, 3, 4 • Recommendation to minimize the potential to develop infectious endophthalmitis associated with an intravitreal injection is included in SmPC section 6.6. • Pack size: one vial or one PFS for single use only. • Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections. <u>Additional risk minimisation measures</u>: Educational plan for adult patients.
Important Identified Risks: Intraocular inflammation	
Risk minimisation measures	<u>*Routine risk communication*</u>: • SmPC Sections 4.3, 4.4.

	• PL Sections 2, 4. • Pack size: one vial or one PFS for single use only. • Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections. <u>Additional risk minimisation measures</u>: Educational plan for adult patients.
Important Identified Risks: Retinal detachment and retinal tear	
Risk minimisation measures	<u>*Routine risk communication*</u>: • SmPC Sections 4.4, 4.8. • PL Sections 2, 4. • Pack size: one vial or one PFS for single use only. • Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections. <u>Additional risk minimisation measures</u>: Educational plan for adult patients.
Important Identified Risks: Intraocular pressure increase	
Risk minimisation measures	<u>*Routine risk communication*</u>: • SmPC Sections 4.4, 4.8, 4.9. • PL Sections 2, 4 • Recommendation for monitoring and managing both intraocular pressure and the perfusion of the optic nerve head is included in SmPC section 4.4.

	• Pack size: one vial or one PFS for single use only. • Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections. Additional risk minimisation measures: Educational plan 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 Rexatilux.

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

There are no studies required for Rexatilux.

Annex 4 - Specific adverse drug reaction follow-up form

MAH has developed following targeted follow-up questionnaires for following risk:

- Infectious endophthalmitis

Targeted Follow-up Checklist: Infectious 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

  1. If yes, please describe including date of occurrence and affected eye
     - Is the patient immunocompromised?

       ☐ Yes ☐ No ☐ Unknown
  - If yes, please describe

Annex 6 - Details of proposed additional risk minimisation activities

The MAH shall ensure that, following discussions and agreements with the National Competent Authorities in each Member State where Rexatilux is marketed, at launch and after launch all ophthalmological clinics where Rexatilux is expected to be used for treatment of adult patients are provided with an up-to-date patient information pack.

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

The patient information pack

The patient educational material has been developed and distributed to the local representatives of the Marketing Authorization Holder, and from the local organization to the physician who can distribute it further to their patients, in order to support the safe use of ranibizumab. The patient information booklet provides information on the key signs and symptoms of potential adverse reactions, ensuring rapid identification and treatment of these events. Patient information booklets are provided to all ophthalmology clinics where ranibizumab is expected to be used for treatment of adult patients.

The patient information pack should be provided in both the form of patient information booklets and an audio-file that contain following key elements:

- Patient information leaflet
- How to prepare for Rexatilux treatment
- What are the steps following treatment with Rexatilux
- 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 (also available in spoken form in is available. The booklets are provided to the physician for distribution to the patient after ranibizumab is prescribed to them.

The booklets aim to provide adequate patient education on:

- What is nAMD, CNV (including secondary to PM), DR 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.

Patient information packs are prepared nationally, in line with the key important risks defined in the RMP and with each member state's national regulations and legislations. Local MAHs are responsible to convey the key safety messages into the local versions of the educational materials. The submission of the material to the respective member state national authorities should take place before the launch of ranibizumab in a new indication (according to the national legislation in the respective countries), and the distribution of the material to all ophthalmology clinics where ranibizumab is expected to be used for treatment of adult patients.