EU Risk Management Plan for Ranivisio (ranibizumab)

RMP version to be assessed as part of this application:

RMP Version number: **2.0**

Data lock point for this RMP: **27-Sep-2024**

Date of final sign-off: **18-Oct-2024**

Rationale for submitting an updated RMP:

- Update of RMP version 1.0, and addition of Ranivisio pre-filled syringe (PFS)

Summary of significant changes in this RMP:

- Changes from previous version V1.0 to current V2.0: addition of Ranivisio PFS and formal changes based on the updated Lucentis RMP of version 20 to 22.

QPPV name[1]: **Larissa Gutenmacher-Ruf**

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

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

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Part I: Product Overview

The medicinal product is a ranibizumab biosimilar to Lucentis. Like the reference product, it will be available as a 10 mg/mL solution for intravitreal (IVT) injection in a single-dose vial containing 2.3 mg of ranibizumab in 0.23 mL solution and as a pre-filled syringe (PFS). Proposed indications in adults, pharmaceutical form, strength, posology and route of administration are identical to those of Lucentis.

Use in preterm infants for the treatment of retinopathy of prematurity (ROP), which is an approved indication of the originator product, is not proposed, as the stand-alone medical device, a low volume high accuracy syringe, specifically developed by Lucentis' MAH to administer a 0.2 mg paediatric dose (i.e. to deliver a volume of 0.02ml of the 10 mg/mL solution for injection), is not commercially available.

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Ranibizumab
Pharmacotherapeutic group (ATC Code)	S01LA04
Marketing Authorisation Applicant	Midas Pharma GmbH
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	Ranivisio (company code: FYB201)
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	<u>Chemical class:</u> Humanised recombinant monoclonal antibody fab fragment
	<u>Summary of mode of action:</u> Ranibizumab is 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 (wet) form of age-related macular degeneration (nAMD), pathologic myopia (PM) and choroidal neovascularisation (CNV) or to visual impairment caused by either diabetic macular oedema (DME) or macular oedema secondary to retinal vein occlusion (RVO) and

	proliferative diabetic retinopathy (PDR) in adults.
	Important information about its composition: Ranibizumab solution for injection complies with the EMA guideline (EMEA/410/01/rev.3.2004) "Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products". None of the excipients used are of human or animal origin. In addition, the primary container closure system does not pose a risk of transmitting spongiform animal encephalopathy agents.
Hyperlink to the Product Information	Proposed PI: Proposed Product Information in Module 1.3.1
Indication(s) in the EEA	Current: The medicinal product is indicated in adults for: • 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)
	Proposed: Not applicable.
Dosage in the EEA	Current: The medicinal product must be administered by a qualified ophthalmologist experienced in intravitreal injections. The recommended dose of 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, 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 branch retinal vein occlusion (RVO)* 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. *Ranibizumab and verteporfin photodynamic therapy in CNV secondary to PM* There is no experience of concomitant administration of ranibizumab and verteporfin.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Solution for injection, 10 mg/mL. Each single-dose vial contains 2.3 mg 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. One pre-filled syringe contains 0.165 ml, equivalent to 1.65 mg ranibizumab. This provides a usable amount to deliver a single dose of 0.05 ml containing 0.5 mg ranibizumab.
	Proposed: Not applicable

Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

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

According to GVP - Module V, this section is not applicable for biosimilar medicinal products.

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

Data from the originator:

Table SII.1: Key safety findings of Lucentis from non-clinical studies and relevance to human usage of ranibizumab

Key safety findings (from non-clinical studies)	Relevance to human usage of ranibizumab
Toxicity: • Key issues identified from acute or repeat-dose toxicity studies Bilateral IVT administration of ranibizumab to cynomolgus monkeys at doses between 0.25 mg/eye and 2.0 mg/eye once every two weeks for up to 26 weeks resulted in dose-dependent ocular effects. Intraocularly, there were dose-dependent increases in anterior chamber flare and cells with a peak two days after injection. The severity of the inflammatory response generally diminished with subsequent injections or during recovery. In the posterior segment, there were vitreal cell infiltration and floaters, which also tended to be dose-dependent and generally persisted to the end of the treatment period. In the 26-week study, the severity of the vitreous inflammation increased with the number of injections. However, evidence of reversibility was observed after recovery. The nature and the timing of the posterior segment inflammation is suggestive of an immune-mediated antibody response to a humanised protein, which may be clinically irrelevant. Cataract formation was observed in some animals after a relatively long period of intense inflammation, suggesting that the lens changes were secondary to severe inflammation. A transient increase in post-dose intraocular pressure (IOP) was observed following IVT injections, irrespective of dose. Microscopic ocular changes were related to inflammation and did not indicate degenerative processes. Granulomatous	Intraocular inflammation and transient increases in IOP are identified risks following IVT administration of ranibizumab. These events are followed in the RMP, the periodic safety update report (PSUR), and are also included in Section 4.4 'Special warnings and precautions for use' in the ranibizumab Summary of Product Characteristics (SmPC).

inflammatory changes were noted in the optic disc of some eyes. These posterior segment changes diminished, and in some instances resolved, during the recovery period. Following IVT administration, no signs of systemic toxicity were detected. Serum and vitreous antibodies to ranibizumab were found in a subset of treated animals.	
• Reproductive/development toxicity The potential of ranibizumab to affect embryo-foetal and/or placental development has been investigated in pregnant cynomolgus monkeys given bilateral IVT injections of ranibizumab every 14 days. Due to restrictions dictated by the IVT route of administration, the doses used (up to 1.0 mg/eye) did not allow to reach maternal toxicity but only a multiple with respect to human systemic exposure. Under these conditions, ranibizumab treatment did not elicit developmental toxicity or teratogenicity, and had no effect on weight or structure of the placenta.	For ranibizumab, no clinical data on exposed pregnancies are available. The systemic exposure to ranibizumab is low after ocular administration, but due to its mechanism of action, ranibizumab must be regarded as potentially teratogenic and embryo-/fetotoxic. Studies in cynomolgus monkeys do not indicate direct or indirect harmful effects with respect to pregnancy or embryonal/foetal development. As the embryo-foetal development investigations were performed in healthy pregnant animals and disease (such as e.g. diabetes) may modify the permeability of the placenta towards a Fab fragment, ranibizumab should be used with caution in women of childbearing potential in general, and during pregnancy, in particular. In the SmPC Section 4.6 'Fertility, pregnancy and lactation' it is stated that women of childbearing potential should use effective contraception during treatment and that, for women who wish to become pregnant and have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child.

Source: Lucentis RMP version 22, Table 3-1

Data from the biosimilar:

A non-clinical study was conducted to evaluate the pharmacokinetics and the ocular tolerance and systemic toxicity of a single 50 µL IVT injection of FYB201 drug product in comparison with EU-approved Lucentis and US-licensed Lucentis over a 2-week period in albino New Zealand White rabbits (study number FYB201 PK201501). The study was divided into two parts: Part A for ocular tolerance and systemic toxicity assessment (N=12) and Part B for analysis of pharmacokinetics (N=54).

For the pharmacokinetic analysis, vitreous humour, aqueous humour, and serum were collected from treatment-naïve rabbits and the concentrations of FYB201, EU-authorised Lucentis, and US-licensed Lucentis were determined. The results showed similar pharmacokinetics (area under the concentration-time curve, mean residence time, concentration half-life $T_{1/2}$) between the products.

In addition, the ocular tolerance and systemic toxicity of the three medicinal products were compared demonstrating that FYB201 and the reference products have similar safety profiles.

Conclusion

Based on these results and on comprehensive analytical similarity data confirming high similarity on structural, physicochemical and functional levels between FYB201 and Lucentis, it is concluded that the key safety findings of Lucentis from non-clinical studies and their relevance to human usage are also applicable to FYB201. Since Lucentis has been thoroughly investigated in terms of safety and sufficient non-clinical and clinical data on ranibizumab have been published in the past ten years, it is justified to assume that based on biosimilarity, FYB201 is a medicinal product with a favourable safety profile and similar safety concerns as Lucentis.

Part II: Module SIII - Clinical trial exposure

One comparative clinical trial in 477 patients (more trial details see further below) was performed to show similar efficacy and safety between the biosimilar and the reference product. This trial therefore provides limited information on clinical exposure.

In line with the concept of biosimilarity the clinical exposure collected with the originator product is relevant also to the biosimilar and is thus included as valuable information.

Data from the originator:

This subsection provides an overview on the drug exposure from the originator's clinical trials, pooled within each indication, as presented in the Lucentis EU RMP version 22.0. Although the originator's indication 'retinopathy of prematurity (ROP)' is not applicable to FYB201, which is proposed for the use in adult patients only, exposure data of preterm infants and patients <18 years are maintained in this section for the sake of completeness.

Table SIII.1: Estimated cumulative subject exposure to ranibizumab by age and gender (safety population)

Indication	Age Group (years except for preterm infants as gestation age in weeks)*	Male		Female		Total	
		Subjects n (%)	Number of injections (% total)	Subjects n (%)	Number of injections (% total)	Subjects n (%)	Number of injections (% total)
nAMD	<50	1 (0.02)	2 (0.005)	3 (0.05)	8 (0.01)	4 (0.04)	10 (0.01)
	50 - <65	490 (11.2)	5444 (12.7)	461 (7.8)	4698 (8.7)	951 (9.3)	10142 (10.5)
	65 - <75	1266 (28.9)	12767 (29.7)	1332 (22.7)	13369 (24.8)	2598 (25.3)	26136 (27.0)
	75 - <85	2031 (46.4)	19783 (46.0)	2856 (48.6)	25990 (48.2)	4887 (47.7)	45773 (47.2)
	≥85	587 (13.4)	4991 (11.6)	1228 (20.9)	9832 (18.2)	1815 (17.7)	14823 (15.3)
	Mean age (SD)	75.6 (8.45)	-	77.7 (8.37)	-	76.8 (8.46)	-
	Total	4375 (100)	42987 (100)	5880 (100)	53897 (100)	10255 (100)	96884 (100)
DME	<55	254 (22.3)	4283 (21.1)	152 (17.1)	2653 (17.7)	406 (20.0)	6936 (19.7)
	55 - <65	407 (35.7)	7190 (35.5)	384 (43.3)	6266 (41.7)	791 (39.0)	13456 (38.2)
	65 - <75	383 (33.6)	6845 (33.8)	266 (30.0)	4887 (32.5)	649 (32.0)	11732 (33.3)
	≥75	96 (8.4)	1933 (9.5)	85 (9.6)	1213 (8.1)	181 (8.9)	3146 (8.9)
	Mean age (SD)	61.7 (9.90)		62.4 (9.48)		62.0 (9.72)	
	Total	1140 (100)	20251 (100)	887 (100)	15019 (100)	2027 (100)	35270 (100)
RVO	<55	309 (24.6)	2751 (21.7)	184 (18.2)	1503 (14.7)	493 (21.7)	4254 (18.5)
	55 - <65	380 (30.2)	3782 (29.8)	275 (27.2)	2666 (26.0)	655 (28.9)	6448 (28.1)
	65 - <75	316 (25.1)	3430 (27.0)	304 (30.0)	3326 (32.4)	620 (27.3)	6756 (29.5)
	≥75	250 (19.9)	2710 (21.4)	249 (24.6)	2756 (26.9)	499 (22.0)	5466 (23.8)
	Unknown**	2 (0.2)	14 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)	14 (0.1)
	Mean age (SD)	62.8 (12.78)		65.8 (12.05)		64.1 (12.54)	
	Total	1257 (100)	12687 (100)	1012 (100)	10251 (100)	2269 (100)	22938 (100)
PM	<45	74 (36.1)	275 (36.8)	99 (19.8)	349 (16.9)	173 (24.6)	624 (22.2)
	45 - <55	36 (17.6)	136 (18.2)	126 (25.3)	488 (23.6)	162 (23.0)	624 (22.2)
	55 - <65	64 (31.2)	242 (32.4)	167 (33.5)	748 (36.2)	231 (32.8)	990 (35.2)
	65 - <75	25 (12.2)	71 (9.5)	92 (18.4)	425 (20.6)	117 (16.6)	496 (17.6)

Indication	Age Group (years except for preterm infants as gestation age in weeks)*	Male		Female		Total	
		Subjects n (%)	Number of injections (% total)	Subjects n (%)	Number of injections (% total)	Subjects n (%)	Number of injections (% total)
	≥75	6 (2.9)	23 (3.1)	15 (3.0)	54 (2.6)	21 (3.0)	77 (2.7)
	Mean age (SD)	50.4 (14.02)		54.3 (12.52)		53.1 (13.09)	
	Total	205 (100)	747 (100)	499 (100)	2064 (100)	704 (100)	2811 (100)
CNV	<18	1 (1.1)	2 (0.3)	4 (4.5)	17 (3.5)	5 (2.8)	19 (1.8)
	18 - <45	24 (27.6)	107 (18.4)	26 (29.2)	93 (19.4)	50 (28.4)	200 (18.9)
	45 - <55	22 (25.3)	154 (26.5)	17 (19.1)	97 (20.2)	39 (22.2)	251 (23.7)
	55 - <65	15 (17.2)	106 (18.2)	14 (15.7)	84 (17.5)	29 (16.5)	190 (17.9)
	65 - <75	18 (20.7)	150 (25.8)	17 (19.1)	117 (24.4)	35 (19.9)	267 (25.2)
	≥75	7 (8.0)	62 (10.7)	11 (12.4)	72 (15.0)	18 (10.2)	134 (12.6)
	Mean age (SD)	53.3 (15.05)	-	52.7 (18.55)	-	53.0 (16.87)	
	Total	87 (100)	581 (100)	89 (100)	480 (100)	176 (100)	1061 (100)
Extended indications	<18	1 (0.9)	12(1.6)	2 (2.9)	22 (4.6)	3(1.7)	34 (2.8)
	18 - <45	16 (14.7)	109 (14.8)	4 (5.8)	25 (5.2)	20 (11.2)	134 (11.0)
	45 - <55	21 (19.3)	152 (20.7)	8 (11.6)	41 (8.6)	29 (16.3)	193 (15.9)
	55 - <65	22 (20.2)	201 (27.3)	18 (26.1)	145 (30.4)	40 (22.5)	346 (28.5)
	65 - <75	29 (26.6)	152 (20.7)	15 (21.7)	110 (23.1)	44 (24.7)	262 (21.6)
	≥75	20 (18.3)	110 (14.9)	22 (31.9)	134 (28.1%)	42 (23.6)	244 (20.1)
	Mean age (SD)	60.4 (15.55)	-	64.5 (15.82)	-	62.0 (15.74)	-
	Total	109 (100)	736 (100)	69 (100)	477 (100)	178 (100)	1213 (100)
PDR	<65	100 (92.6)	1103 (92.8)	73 (88.0)	699 (88.0)	173 (90.6)	1802 (90.9)
	≥65	8 (7.4)	86 (7.2)	10 (12.0)	95 (12.0)	18 (9.4)	181 (9.1)
	Mean age (SD)	49.8 (10.79)	-	51.3 (12.34)	-	50.4 (11.480)	-
	Total	108 (100)	1189 (100)	83 (100)	794 (100)	191 (100)	1983 (100)
ROP (preterm infants)	≤24	32 (42.1)	72 (38.9)	31 (36 0)	84 (39.6)	63 (38.9)	156 (39.3)
	>24 - <27	20 (26.3)	51 (27.6)	21 (24.4)	45 (21.2)	41 (25.3)	96 (24.2)

Indication	Age Group (years except for preterm infants as gestation age in weeks)*	Male		Female		Total	
		Subjects n (%)	Number of injections (% total)	Subjects n (%)	Number of injections (% total)	Subjects n (%)	Number of injections (% total)
	≥27	24 (31.6)	62 (33.5)	34 (39.5)	83 (39.2)	58 (35.8)	145 (36.5)
	Mean age (SD)	25.6 (2.13)	-	26.3 (2.60)	-	26.0 (2.40)	-
	Total	76 (100)	185 (100)	86 (100)	212 (100)	162 (100)	397 (100)

*Age is presented in years for all indications except for preterm infants (ROP). For these patients, age is presented as gestational age at birth in weeks.
Age is unknown for 2 subjects from RVO indication and these subjects received 14 injections.
Source: Lucentis RMP version 22.0, Table 4-1

Table SIII.2: Estimated cumulative subject exposure to ranibizumab by race (safety population)

Indication	**Ranibizumab Dose Level**	**Subjects n (%)**	**Number of injections (% total)**
nAMD	Asian	790 (7.7)	9688 (10.0)
	Black	23 (0.2)	191 (0.2)
	Caucasian	9246 (90.2)	85360 (88.1)
	Other	187(1.8)	1497 (1.5)
	Unknown	9 (0.1)	148 (0.2)
	Total	10255 (100)	96884 (100)
DME	Asian	613 (30.2)	5254 (14.9)
	Black	89 (4.4)	2358 (6.7)
	Caucasian	1280 (63.1)	26658 (75.6)
	Other	28 (1.4)	475 (1.3)
	Unknown	17 (0.8)	525 (1.5)
	Total	2027 (100)	35270 (100)
RVO	Asian	575 (25.3)	4051 (17.7)
	Black	96 (4.2)	999 (4.4)
	Caucasian	1525 (67.2)	17090 (74.5)
	Other	31 (1.4)	346 (1.5)
	Unknown	42 (1.9)	452 (2.0)
	Total	2269 (100)	22938 (100)
PM	Asian	550 (78.1)	2170 (77.2)
	Caucasian	153 (21.7)	639 (22.7)
	Other	1 (0.1)	2 (0.1)
	Total	704 (100)	2811 (100)
CNV	Asian	11 (6.4)	27 (2.5)
	Black	1 (0.6)	5 (0.5)
	Caucasian	157 (89.2)	968 (91.2)
	Other	7 (4.0)	61 (5.7)
	Total	171 (100)	1061 (100)
Extended indications	Asian	17 (9.6)	99 (8.2)
	Black	2 (1.1)	11 (0.9)
	Caucasian	154 (88.2)	1088 (89.7)
	Other	2 (1.1)	15 (1.2)
	Total	178 (100)	1213 (100)
Total (adults)	Asian	2925 (18.2)	23471 (14.4)
	Black	216 (1.3)	3576 (2.2)
	Caucasian	12616 (78.4)	132042 (81.2%)
	Other	266 (1.7)	2418 (1.5)
	Unknown	68 (0.4)	1125 (0.7)
	Total	16091 (100)	162632 (100)
PDR	Asian	2 (1.0)	21 (1.1)
	Black	40 (20.9)	402 (20.3)
	Caucasian	135 (70.7)	1397 (70.4)
	Other	2 (1.0)	27 (1.4)
	Unknown	12 (6.3)	136 (6.9)

Indication	Ranibizumab Dose Level	Subjects n (%)	Number of injections (% total)
	Total	191 (100)	1983 (100)
ROP (preterm infants)	Asian	49 (30.2)	124 (31.2)
	Black	5 (3.1)	12 (3.0)
	Caucasian	98 (60.5)	239 (60.2)
	Other	10 (6.2)	22 (5.5)
	Total	162 (100)	397 (100)

Source: Lucentis RMP version 22.0, Table 4-2

Data from the biosimilar:

A 12-month, randomised, active-controlled, evaluation-masked, parallel-group, multicentre, Phase III trial was conducted to evaluate the *Efficacy and Safety of the Biosimilar Ranibizumab FYB201 in Comparison to Lucentis in Patients with Neovascular Age-Related Macular Degeneration (COLUMBUS-AMD).* It was designed to demonstrate clinical equivalence in terms of efficacy and safety of FYB201 with US-licensed Lucentis in the treatment of patients with subfoveal nAMD.

In total, 477 patients were randomised in the study at 75 sites and 12 countries. The study duration for each subject was approximately 12 months involving 12 consecutive IVT injections of 0.5 mg Lucentis or FYB201 every month to newly diagnosed nAMD patients.

Summary information on the clinical trial exposure is provided in the tables below.

Table SIII.3: Total number of injections per patient

No. of injections	FYB201 (N=238)	Lucentis (N=239)	Total (N=477)
1	3 (1.3%)	1 (0.4%)	4 (0.8%)
2	1 (0.4%)	0 (0.0%)	1 (0.2%)
3	1 (0.4%)	1 (0.4%)	2 (0.4%)
4	2 (0.8%)	1 (0.4%)	3 (0.6%)
5	0 (0.0%)	1 (0.4%)	1 (0.2%)
6	1 (0.4%)	4 (1.7%)	5 (1.0%)
7	1 (0.4%)	2 (0.8%)	3 (0.6%)
8	0 (0.0%)	3 (1.3%)	3 (0.6%)
9	2 (0.8%)	3 (1.3%)	5 (1.0%)
10	6 (2.5%)	9 (3.8%)	15 (3.1%)
11	22 (9.2%)	25 (10.5%)	47 (9.9%)
12	199 (83.6%)	189 (79.1%)	388 (81.3%)

Source: CSR Table 14.3.1.4

Table SIII.4: Age group and gender

	FYB201 (N=238)		Lucentis (N=239)		Total (N=477)
Age range (years)	**Male**	**Female**	**Male**	**Female**	
50 – 64	16 (6.7%)	9 (3.8%)	11 (4.6%)	8 (3.3%)	44 (9.2%)
65 – 74	34 (14.3%)	44 (18.5%)	37 (15.5%)	33 (13.8%)	148 (31.0%)
75 – 84	38 (16.0%)	65 (27.3%)	46 (19.2%)	72 (30.1%)	221 (46.3%)
>85	15 (6.3%)	17 (7.1%)	11 (4.6%)	21 (8.8%)	64 (13.4%)
Total	**103 (43.3%)**	**135 (56.7%)**	**105 (43.9%)**	**134 (56.1%)**	

Source: Analysis by age gender treatment group, Final v02, 28-May-2020

Table SIII.5: Ethnic origin

Race [n (%)]	**FYB201 (N=237)**	**Lucentis (N=238)**	**Total (N=475)**
White	235 (99.2%)	232 (97.5%)	467 (98.3%)
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Black or African American	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	0 (0.0%)	2 (0.8%)	2 (0.4%)
Native Hawaiian or other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	2 (0.8%)	4 (1.7%)	6 (1.3%)

Source: CSR Table 14.1.2.1.3 FAS_US

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

The only known mechanism of action of ranibizumab is its high affinity binding to all VEGF-A isoforms and their degradation products, thereby preventing binding of VEGF-A to its receptors VEGFR1 and VEGFR2 on the surface of endothelial cells. 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, PM and CNV or to visual impairment caused by either DME or macular oedema secondary to RVO. The therapeutic effect of ranibizumab in the intended indications is essentially based on this mechanism of action. Biosimilarity of FYB201 to Lucentis was clinically confirmed in the pivotal COLUMBUS-AMD study involving 477 patients with nAMD treated with IVT injections of ranibizumab for up to 48 weeks. The overall evaluation of tolerability and safety in the COLUMBUS-AMD study confirmed the known safety profile for ranibizumab; there was no trend for imbalance between FYB201 and Lucentis in any of the safety assessments, including immunogenicity.

The results of the COLUMBUS-AMD study, which was conducted in patients with nAMD, the most sensitive population, demonstrate similar clinical efficacy and safety compared to the reference medicinal product, and in compliance with the requirements for extrapolation to other indications of the reference medicinal product (EMA/CHMP/BMWP/403543/2010), provide the clinical basis for the extrapolation to the following indications that have not been specifically studied in the clinical development:

In adult patients:

- The treatment of visual impairment due to DME

- The treatment of PDR
- The treatment of visual impairment due to macular oedema secondary to RVO (branch RVO or central RVO)
- The treatment of visual impairment due to CNV

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

Any prior treatment with IVT anti-VEGF agent (e.g. bevacizumab, aflibercept, ranibizumab) in either eye

Reason for exclusion: Use of these agents could interfere with interpretation of the clinical outcomes.

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

Rationale: To study ranibizumab only in treatment-naïve patients.

History of vitrectomy, macular surgery or other surgical intervention for AMD in the study eye

Reason for exclusion: Vitreoretinal surgery is associated with the removal of the vitreous gel; thus, it may influence the pharmacodynamics of an intraocular pharmacological treatment. Precautionary measure due to limited data in patients with vitrectomised eyes. Macular surgery and other surgical interventions may also hinder interpretation of study outcomes, e.g. foveal centre point (FCP) or foveal central subfield (FCS) assessment.

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

Rationale: To exclude confounding factors that may hinder interpretation of study results.

History of IVT or periocular injections of corticosteroids or device implantation within six months prior to Screening in the study eye

Reason for exclusion: The use of corticosteroids has a potential impact on the efficacy results, can cause morphology changes of the eye, and may affect the biosimilarity evaluation.

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

Prior treatment with verteporfin (photodynamic therapy), transpupillary thermotherapy, radiation therapy, or retinal laser treatment (e.g. focal laser photocoagulation) in the study eye

Reason for exclusion: Precautionary measure. Use of these agents could interfere with interpretation of the clinical outcomes.

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

Rationale: To study ranibizumab only in treatment-naïve patients

Topical ocular corticosteroids administered for at least 30 consecutive days within three months prior to Screening

Reason for exclusion: The use of topical corticosteroids has a potential impact on the efficacy results, can cause morphology changes of the eye, and may affect the biosimilarity evaluation.

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

Any other intraocular surgery (including cataract surgery) in the study eye within three months prior to Screening

Reason for exclusion: According to the SmPC of the reference product, the ranibizumab dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of performed or planned intraocular surgery

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

Rationale: Precautionary measure

Sub- or intra-retinal haemorrhage that comprises more than 50% of the entire lesion in the study eye

Reason for exclusion: Large sub- or intra-retinal haemorrhage can confound the assessment of the extent and size of the neovascular lesion that needs treatment. Furthermore, it is listed as special warning in the SmPC of the originator.

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

Rationale: Not to include patient with disease features that would confound or make the results difficult to interpret

Fibrosis or atrophy involving the centre of the fovea or influencing central visual function in the study eye

Reason for exclusion: These anatomic characteristics are representative of pre-existing pathology, which make interpretation of patient data obtained during a clinical trial difficult and may confound study results.

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

Rationale: Ranibizumab is unlikely to have an effect in patients with pre-existing pathology from late stage disease

CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia

Reason for exclusion: CNV with other origins may have a potential impact on best corrected visual acuity and other functional parameters and eventually could interfere with the interpretation of the clinical outcomes

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

Retinal pigment epithelial tear involving the macula in the study eye

Reason for exclusion: Retinal pigment epithelial tear is listed as common adverse drug reaction in the SmPC of the reference medicinal product. Worsening of the condition due to the injection procedure is possible.

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

Rationale: To exclude the risk of worsening the condition.

History of full-thickness macular hole (stage 2 and above by clinical examination or full thickness macular hole by SD-OCT imaging of any size) in the study eye

Reason for exclusion: A patient's macular hole may cause a decline in visual acuity, an important endpoint for safety and efficacy of an intervention for intraocular use. Therefore, the presence of a macular hole could confound efficacy outcomes. The section "4.4 Special warning and precautions for use" of the Lucentis SmPC includes the recommendation to discontinue the treatment in patients with stage 3 or 4 macular hole as only limited data are available.

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

History of retinal detachment in the study eye

Reason for exclusion: Precautionary measure. These anatomic characteristics are representative of pre-existing pathology, which make interpretation of patient data obtained during a clinical trial difficult and may confound study results.

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

Rationale: To exclude patients with pre-existing pathology, which make interpretation of patient data obtained during a clinical trial difficult and may confound study results.

Current vitreous haemorrhage in the study eye

Reason for exclusion: Precautionary measure. This anatomic characteristic is representative of pre-existing pathology, which make interpretation of patient data obtained during the clinical trial difficult and may confound study results.

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

Rationale: To exclude patients with pre-existing pathology, which make interpretation of patient data obtained during a clinical trial difficult and may confound study results.

Spherical equivalent of the refractive error in the study eye demonstrating more than 8 dioptres of myopia

Reason for exclusion: Refractive errors with high dioptre values can make interpretation of patient data obtained during the clinical trial difficult and may confound study results.

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

For patients who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye cannot exceed 8 dioptres of myopia

Reason for exclusion: Refractive errors with high dioptre values can make interpretation of patient data obtained during the clinical trial difficult and may confound study results.

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

History of corneal transplant in the study eye

Reason for exclusion: Corneal transplant may confound study results and make interpretation of patient data obtained during a clinical trial difficult.

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

Aphakia in the study eye. Absence of an intact posterior capsule is allowed if it occurred as a result of YAG laser posterior capsulotomy in association with prior posterior chamber intraocular lens implantation

Reason for exclusion: Aphakia is a potential confounding factor which may impact biosimilarity assessment

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

Active or recent (within 4 weeks) intraocular inflammation of clinical significance in the study eye such as active infections of the anterior segment (excluding mild blepharitis) including conjunctivitis, keratitis, scleritis, uveitis or endophthalmitis

Reason for exclusion: There is a risk of worsening of an ongoing inflammatory process, or masking inflammation due to another cause. In addition, active intraocular inflammation may be associated with an increased IOP; administering an intraocular injection when there is ongoing inflammation is contraindicated.

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

Rationale: Active severe intraocular inflammation is a contraindication mentioned in the SmPC of the originator.

Uncontrolled hypertension or glaucoma in the study eye (defined as IOP ≥30 mmHg, despite treatment with anti-glaucomatous medication)

Reason for exclusion: Precautionary measure. Increased IOP and uncontrolled glaucoma is a general contraindication to any invasive intraocular procedure due to known possible associated complications.

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

Rationale: Injection of additional volume to the vitreous in patients with increased IOP or uncontrolled glaucoma should generally be avoided to avoid consequences of additional raised IOP including a temporary increase associated with the procedure.

Ocular disorders in the study eye (i.e. retinal detachment, pre-retinal membrane of the macula or cataract with significant impact on visual acuity) at the time of enrolment

Reason for exclusion: Ocular disorders may confound interpretation of study results and compromise visual acuity

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

Any concurrent intraocular condition in the study eye (e.g. glaucoma, cataract or diabetic retinopathy) that, in the opinion of the Investigator, would either require surgical intervention during the study to prevent or treat visual loss that might result from that condition or affect interpretation of study results.

Reason for exclusion: Any condition which may lead to loss of vision or associated potential complications could confound the outcomes of efficacy and safety in the clinical trial.

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

Rationale: Precautionary measure and to exclude confounding factors that may hinder the interpretation of study results.

Use of other investigational drugs (excluding vitamins, minerals) within 30 days or 5 half-lives from Screening, whichever is longer

Reason for exclusion: General exclusion criterion to avoid potential risk factors and unknown side effects

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

Rationale: Standard exclusion in clinical trials to exclude confounding effects

Any type of advanced, severe or unstable disease, including any medical condition (controlled or uncontrolled) that could be expected to progress, recur, or change

Reason for exclusion: Exclusion of any diseases that may bias the assessment of the clinical status of the patient to a significant degree or put the patient at special risk

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

Rationale: Precautionary measure

Stroke or myocardial infarction within three months prior to Screening

Reason for exclusion: Precautionary measure based on effects which have been identified following intravenous administration of VEGF inhibitors.

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

Rationale: Precautionary measure to exclude patients with a recent event of cerebral vascular accident or myocardial infarction

Presence of uncontrolled systolic blood pressure >160 mmHg or uncontrolled diastolic blood pressure >100 mmHg

Reason for exclusion: Precautionary measure as systemic conditions such as uncontrolled hypertension are serious risks impacting the patient's overall health. When the patient is undergoing treatment for serious systemic conditions, study participation and required follow-up visits may be difficult to make.

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

Rationale: To exclude patients with poor control of high blood pressure that may impact overall health and their ability to meet the requirements for study visits and assessments.

Known hypersensitivity to the investigational drug (ranibizumab or any component of the ranibizumab formulation) or to drugs of similar chemical class or to fluorescein or any other component of fluorescein formulation

Reason for exclusion: Hypersensitivity to ranibizumab would potentially elicit a severe reaction. Although allergic reactions such as rash, urticaria, pruritus and erythema have been seen following treatment with ranibizumab, there are a number of concurrently administered agents during the injection procedure which could also be the cause of a hypersensitivity reaction (e.g. topical anaesthetics or antibiotics, dilating drops such as phenylephrine, or rarely, povidone-iodine)

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

Rationale: Hypersensitivity to the active substance or to any of the excipients is a contraindication mentioned in the Lucentis SmPC.

Current or planned use of systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine (Plaquenil®), tamoxifen, phenothiazines and ethambutol

Reason for exclusion: Substances that are toxic to the lens can make the assessment and following interpretation of patient data obtained during the clinical trial difficult and may confound study results.

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

History of recurrent significant infections and/or current treatment for active systemic infection

Reason for exclusion: A systemic infection could spread into the eye through hematogenous circulation and confound study results. Also, the presence of systemic infection may put the patient at higher risk for infection related to the intraocular injection.

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

Rationale: Precautionary measure.

Systemic treatment with high doses of corticosteroids (administration of >10 mg/day of prednisolone equivalent) during the last six months prior to Screening

Reason for exclusion: High doses of systemic corticosteroids may have an impact on the study results and confound their interpretation

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

Any diagnosis and/or signs of nAMD requiring treatment with an IVT anti-VEGF agent (e.g. aflibercept, bevacizumab, ranibizumab) within the screening period or at study treatment initiation (Visit 1) in the fellow eye.

Reason for exclusion: Treatment of the fellow eye should not be withheld if it is crucial. However, treated fellow eyes that are not studied during the clinical trial may have an impact on the pharmacokinetic results and confound their interpretation

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

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.

Over the originator's interventional clinical programme, approximately 16,091 adult patients (indications: nAMD, CNV, DME, RVO) were exposed up to 05 October 2021. A total of 162 paediatric patients (indication: ROP) were exposed in the pivotal RAINBOW study. The clinical development programme of the originator product includes studies (e.g. RISE and RIDE [Brown et al. 2013]) with Lucentis that support safety of ranibizumab during long-term treatment. From the international birth date of the originator through 31 May 2018, approximately 50 million vials and PFSs of ranibizumab have been sold (≈8,2 million patient years; source: RMP Lucentis version 22.0).

This long marketing experience of the originator, together with results of the clinical development programme, are greatly increasing the probability that rare ADRs have been detected in the years during which the product has been administered. ADRs listed for the originator are reflected in the proposed SmPC of FYB201, based on the conclusion of similar safety profiles.

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

Table SIV.1: Exposure of special populations included or not in clinical trial development programmes of ranibizumab

Type of special population	Exposure
Pregnant women	not included in the clinical development programme
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	not included in the clinical development programme
Population with relevant different ethnic origin	Please refer to Table SIII.2 and SIII.5
Subpopulations carrying relevant genetic polymorphisms	not included in the clinical development programme

Part II: Module SV - Post-authorisation experience

Not applicable.

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

Potential for misuse for illegal purposes

Ranibizumab as an anti-VEGF agent has no potential effects that would promote misuse for illegal purposes. Furthermore, ranibizumab will only be available by prescription and administered as an IVT injection by health care professionals. The access for other than recommended indications will be limited by this restriction. No additional measures are suggested to prevent misuse.

Part II: Module SVII - Identified and potential risks

FYB201 and the reference product Lucentis were well tolerated in the conducted COLUMBUS-AMD study. There were no clinically remarkable differences in the incidence and nature of treatment-emergent adverse events. The overall evaluation of tolerability and safety confirmed the known safety

profile for ranibizumab; there was no trend for imbalance between FYB201 and Lucentis in any of the safety assessments, including immunogenicity. In addition, no new or unknown adverse events were observed. Therefore, the same identified and potential risks of Lucentis for adult patients published in the risk management summary are applied to FYB201. Safety concerns of the originator related to the indication 'retinopathy of prematurity (ROP)' in preterm infants, namely the important potential risk 'neurodevelopmental impairment (ROP)' and the missing information 'long-term safety of ranibizumab in the condition ROP', are not included because FYB201 is proposed for the use in adult patients only.

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. Biosimilarity of FYB201 to Lucentis was demonstrated in the COLUMBUS-AMD study conducted by the applicant. The overall evaluation of tolerability and safety of FYB201 confirmed the known safety profile for ranibizumab; there was no trend for imbalance between FYB201 and Lucentis in any of the safety assessments including immunogenicity. In addition, no new or unknown adverse events were observed.

Reason for not including an identified or potential risk 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

The safety concerns in this initial RMP submission for FYB201 are identical to the current safety concerns of Lucentis (EPAR - Risk-management-plan summary, updated: 14/12/2021) for adult patients, that comprise the important identified risks: infectious endophthalmitis, intraocular inflammation, retinal detachment and retinal tear, intraocular pressure increase.

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

Important Identified Risk: Infectious endophthalmitis

Potential mechanisms:

IVT 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 a loss of vision and sometimes even to the loss of the eye itself.

Characterisation of the risk:

Endophthalmitis following IVT injections of anti-VEGF agents is an uncommon but potentially devastating complication [Sachdeva et al. 2016]. An estimate of the rate of endophthalmitis associated with IVT ranibizumab is 1 in 4,500 injections [Fintak et al. 2008].

For the originator product Lucentis (source: RMP version 22.0), reported frequencies from pooled clinical trials are given as absolute number, percentage, and 95% confidence intervals (Clopper Pearson exact method):

- In *adults* in the indication nAMD in studies of
    - up to 1 year duration: 0 (0.0) (0.0, 13.3) to 4 (0.9) (0.2, 2.3)
    - >1 year up to 3 years duration: 0 (0.0) (0.0, 7.4) to 7 (1.6) (0.6, 3.3)
- In *adults* in the indication visual impairment due to DME in studies of
    - up to 1 year duration: 4 (0.6) (0.2, 1.6)
    - >1 year up to 3 years duration: 0 (0.0) (0.0, 3.5)
- In *adults* in the indication visual impairment due to macular oedema secondary to RVO in studies of
    - up to 1 year duration: 0 (0.0) (0.0, 9.2) to 1 (0.5) (0.0, 2.9)
    - >1 year up to 2 years duration: 0 (0.0) (0.0, 1.7)
- In *adults* in the indication visual impairment due to CNV in studies of
    - up to 1 year duration: 0 (0.0) (0.0, 2.5) to 1 (0.8) (0.0, 4.6)
- In *adults* in the indication PDR in studies of
    - Up to 2 years duration: 1 (0.5) (0.0 to 2.9)

The frequency of the treatment-emergent adverse events (TEAEs) 'infectious endophthalmitis' in the COLUMBUS-AMD trial was uncommon and comparable between treatment groups.

Table SVII.1: Infectious endophthalmitis in the COLUMBUS-AMD trial

Adverse events	**FYB201 0.5 mg (N=238) n (%)**	**Lucentis 0.5 mg (N=239) n (%)**
TEAEs	1 (0.4%)	2 (0.8%)
At least possibly IMP-related TEAEs	0	1 (0.4%) [a]
Worst severity	-	Severe (1)
Seriousness	-	Serious (1)
Worst outcome	-	Recovered/resolved (1)

MedDRA PTs for searching 'infectious endophthalmitis' in the clinical database are specified in Attachment to Annex 7 of RMP v0.1.

[a] endophthalmitis (1)

Source: Attachment to Annex 7 of RMP v0.1, Tables 1.1-1.5

Risk factors and risk groups:

Ranibizumab 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. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

Impact on the risk-benefit balance of the product:

The reporting rate of infectious endophthalmitis following an IVT injection of ranibizumab is low, also in the conducted COLUMBUS-AMD trial, and the benefit-risk balance is assessed as positive.

Public health impact:

The frequency of reported events of infectious endophthalmitis is expected to be comparably low in post-marketing.

Important Identified Risk: Intraocular inflammation

Potential mechanisms:

IVT injections, including those with ranibizumab, have been associated with intraocular inflammation. Proper aseptic injection techniques must always be used when administering ranibizumab.

Evidence source(s) and strength of evidence:

Intraocular inflammation can possibly lead to a loss of vision and sometimes even to the loss of the eye itself.

Characterisation of the risk:

For Lucentis (source: RMP version 22.0), reported frequencies from pooled clinical trials are given as absolute number, percentage, and 95% confidence intervals (Clopper Pearson exact method):

- In *adults* in the indication nAMD in studies of
    - up to 1 year duration: 0 (0.0) (0.0, 13.3) to 90 (20.5) (16.8, 24.5)
    - >1 year up to 3 years duration: 0 (0.0) (0.0, 7.4) to 111 (25.2) (21.2, 29.6)
- In *adults* in the indication visual impairment due to DME in studies of
    - up to 1 year duration: 10 (1.5) (0.7, 2.8)
    - >1 year up to 3 years duration: 4 (4.8) (1.3, 11.9) to 9 (2.8) (1.3, 5.2)
- In *adults* in the indication visual impairment due to macular oedema secondary to RVO in studies of
    - up to 1 year duration: 0 (0.0) (0.0, 9.2) to 42 (16.2) (11.9, 21.3)
    - >1 year up to 2 years duration: 14 (7.8) (4.3, 12.7) to 31 (8.7) (6.0, 12.1)
- In *adults* in the indication visual impairment due to CNV in studies of
    - up to 1 year duration: 2 (1.7) (0.2, 5.9) to 15 (12.6) (7.2, 19.9)
- In *adults* in the indication PDR in studies of
    - up to 2 years duration: 0 (0.0) (0.0, 1,6)

The frequency of the TEAEs 'intraocular inflammation' in the COLUMBUS-AMD trial was common and comparable between treatment groups.

Table SVII.2: Intraocular inflammation in the COLUMBUS-AMD trial

Adverse events	**FYB201 0.5 mg (N=238) n (%)**	**Lucentis 0.5 mg (N=239) n (%)**
TEAEs	20 (8.4%)	20 (8.4%)
At least possibly IMP-related TEAEs	2 (0.8%) [a]	2 (0.8%) [b]
Severity	Mild (1), moderate (1)	Mild (2)
Seriousness	Serious (1), non-serious (1)	Non-serious (2)
Outcome	Recovered/resolved (2)	Recovered/resolved (2)

MedDRA PTs for searching 'intraocular inflammation' in the clinical database are specified in Attachment to Annex 7 of RMP v0.1.

[a] iridocyclitis (1), conjunctivitis (1); [b] punctate keratitis (2)

Source: Attachment to Annex 7 of RMP v0.1, Tables 2.1-2.5

Risk factors and risk groups:

Proper aseptic injection techniques must always be used when administering ranibizumab, and injection must not be given to 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. Patients should be instructed to report any symptoms suggestive of an intraocular inflammation without delay.

Impact on the risk-benefit balance of the product:

The reporting rate of ocular inflammation following an IVT injection of ranibizumab is low, also in the conducted COLUMBUS-AMD trial, and the benefit-risk balance is assessed as positive.

Public health impact:

The frequency of reported events of intraocular inflammation is expected to be comparably low in post-marketing.

Important Identified Risk: Retinal detachment and retinal tear

Potential mechanisms:

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. 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 tumours, 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.

Characterisation of the risk:

For Lucentis (source: RMP version 22.0), reported frequencies from pooled clinical trials are given as absolute number, percentage, and 95% confidence intervals (Clopper Pearson exact method):

- In *adults* in the indication nAMD in studies of
    - up to 1 year duration: 0 (0.0) (0.0, 13.3) to 128 (29.1) (24.9, 33.6)
    - >1 year up to 3 years duration: 0 (0.0) (0.0, 2.7) to 149 (33.9) (29.4, 38.5)
- In *adults* in the indication visual impairment due to DME in studies of
    - up to 1 year duration: 0 (0.0) (0.0, 1.5) to 3 (1.2) (0.2, 3.3)

  - >1 year up to 3 years duration: 0 (0.0) (0.0, 3.5) to 1 (0.6) (0.0, 3.1)
- In *adults* in the indication visual impairment due to macular oedema secondary to RVO: no studies in Lucentis RMP.
- In *adults* in the indication visual impairment due to CNV in studies of
  - up to 1 year duration: 0 (0.0) (0.0, 2.5) to 7 (1.2) (0.5, 2.4)
- In *adults* in the indication PDR in studies of
  - up to 2 years duration: 9 (4.7) (2.2, 8.8)

The frequency of the TEAEs 'retinal detachment and retinal tear' in the COLUMBUS-AMD trial was common and slightly higher in the group treated with Lucentis.

Table SVII.3: Retinal detachment and retinal tear in the COLUMBUS-AMD trial

Adverse events	**FYB201 0.5 mg (N=238) n (%)**	**Lucentis 0.5 mg (N=239) n (%)**
TEAEs	5 (2.1%)	9 (3.8%)
At least possibly IMP-related TEAEs	1 (0.4%) [a]	3 (1.3%) [b]
Worst severity	Moderate (1)	Mild (1), moderate (1), severe (1)
Seriousness	Non-serious (1)	Non-serious (3)
Worst outcome	Not recovered/resolved or recovered/resolved with sequelae (1)	Not recovered/resolved or recovered/resolved with sequelae (3)

MedDRA PTs for searching 'retinal detachment and retinal tear' in the clinical database are specified in the Attachment to Annex 7 of RMP v0.1.

[a] retinal pigment epithelial tear (1); [b] retinal pigment epithelial tear (3)

Source: Source: Attachment to Annex 7 of RMP v0.1, Tables 3.1-3.5

Risk factors and risk groups:

The following conditions might increase the risk for retinal detachment: previous retinal detachment or retinal tear, eye tumours, inflammation in the choroid or the retina, eye injury, or severe high blood pressure.

Preventability:

In most cases, a retinal detachment or retinal tear cannot be prevented. In ROP patients, retinal detachment is associated with advanced stages of the disease and can be prevented by treatment.

Impact on the risk-benefit balance of the product:

Based on the low rate of retinal detachment and retinal tear following an IVT injection of ranibizumab, also in the conducted COLUMBUS-AMD trial, the benefit-risk balance is assessed as positive.

Public health impact:

The number of reported events of retinal detachment and retinal tear is expected to be comparably low in post-marketing.

Important Identified Risk: Intraocular pressure increase

Potential mechanisms:

Following an IVT injection of ranibizumab, a transient increase in IOP may be anticipated. Sustained IOP increases have also been identified. Both IOP and the perfusion of the optic nerve head must be monitored and managed appropriately.

Evidence source(s) and strength of evidence:

The injection of a volume of 50 µL of ranibizumab may lead to an increase in IOP.

Characterisation of the risk:

For Lucentis (source: RMP version 22.0), reported frequencies from pooled clinical trials are given as absolute number, percentage, and 95% confidence intervals (Clopper Pearson exact method):

- In *adults* in the indication nAMD in studies of
    - up to 1 year duration: 1 (4.8) (0.1, 23.8) to 77 (17.5) (14.1, 21.4)
    - up to 3 years duration: 3 (2.7) (0.6, 7.7) to 112 (25.5) (21.4, 29.8)
- In *adults* in the indication visual impairment due to DME in studies of
    - up to 1 year duration: 47 (7.2) (5.3, 9.4)
    - up to 3 years duration: 6 (7.2) (2.7, 15.1) to 22 (6.7) (4.3, 10.0)
- In *adults* in the indication visual impairment due to macular oedema secondary to RVO in studies of
    - up to 1 year duration: 3 (9.7) (2.0, 25.8) to 28 (10.8) (7.3, 15.2)
    - up to 2 years duration: 20 (11.1) (6.9, 16.6) to 61 (17.1) (13.3, 21.4)
- In *adults* in the indication visual impairment due to CNV in studies of
    - up to 1 year duration: 1 (0.8) (0.0, 4.6) to 18 (3.0) (1.8, 4.8)
- In *adults* in the indication PDR in studies of
    - up to 2 years duration: 4 (2.1) (0.6, 5.3)

The frequency of the TEAEs 'intraocular pressure increased' in the COLUMBUS-AMD trial was common and comparable between treatment groups.

Table SVII.4: Intraocular pressure increased in the COLUMBUS-AMD trial

Adverse event	**FYB201 0.5 mg (N=238) n (%)**	**Lucentis 0.5 mg (N=239) n (%)**
TEAEs	12 (5.0%)	12 (5.0%)
At least possibly IMP-related TEAEs	3 (1.3%) [a]	2 (0.8%) [b]
Worst severity	Mild (2), moderate (1)	Mild (2)
Seriousness	Non-serious (3)	Non-serious (2)
Worst outcome	Recovered/resolved (3)	Recovered/resolved (2)

MedDRA PTs for searching 'intraocular pressure increased' in the clinical database are specified in Attachment to Annex 7 of RMP v0.1.

[a] intraocular pressure increased (3); [b] intraocular pressure increased (2)

Source: Attachment to Annex 7 of RMP v0.1, Tables 4.1-4.5

Risk factors and risk groups:

Pre-existing high IOP is a risk factor. Ranibizumab should not be administered in the event of an IOP of ≥30 mmHg.

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 reporting rate of increased IOP following an IVT injection of ranibizumab has been consistent over the years and this risk is well characterised. The benefit-risk balance is assessed as positive for ranibizumab.

Public health impact:

The number of reported events of increased IOP following an IVT injection of ranibizumab is expected to be comparably low in post-marketing.

SVII.3.2. Presentation of the missing information

Not applicable

Part II: Module SVIII - Summary of the safety concerns

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

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

In line with the pharmacovigilance activities of the originator, specific follow-up checklists are provided in Annex 4 of this RMP for the following safety concerns:

- Infectious endophthalmitis

The questionnaire will be used to collect further data to help further characterise and/or closely monitor these safety concerns.

Other forms of routine pharmacovigilance activities for safety concerns:

Follow-up of case reports: The minimum desired case information for ranibizumab 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

In line with the originator, no additional pharmacovigilance activities are proposed.

III.3 Summary Table of additional Pharmacovigilance activities

In line with the originator, no additional pharmacovigilance activities are proposed.

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are planned.

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

Risk Minimisation Plan

The safety information in the proposed product information and the risk minimisation measures are aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

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

Safety concern	Routine risk minimisation activities
Important identified risks	
Infectious endophthalmitis	Routine risk communication: SmPC sections 4.2, 4.3, 4.4, 4.8, 6.6. Package Leaflet (PL) sections 2, 3, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: guidance on how to administer an IVT injection and information for physicians and patients on prevention and management of this event 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 IVT 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 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 IVT 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 IVT injections.
Intraocular pressure increase	Routine risk communication: SmPC Sections 4.4, 4.8, 4.9. PL Section 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: – Notice to monitor and manage both IOP and the perfusion of the optic nerve head appropriately in SmPC section 4.4. 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 IVT injections.

V.2. Additional Risk Minimisation Measures

Educational plan for adult patients in the indications nAMD, CNV, DME, RVO, and PDR (Annex 6)

Objectives:

To ensure that patients are adequately informed about the potential to develop IOP increase, intraocular inflammation, retinal detachment and retinal tear and infectious endophthalmitis after an IVT injection of ranibizumab, a patient information booklet (also available in spoken form in audio format) will be developed in accordance to the reference product. The booklets will be provided to the physician for distribution to the patient after ranibizumab is prescribed to them.

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 important 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 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 (according to the national legislation in the respective countries), and the distribution of the material to all ophthalmology clinics where FYB201 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 minimisation 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 at the time of the PSUR.

Educational materials for adult patients have been in place for the reference product Lucentis since its launch, and since further studies to assess continued effectiveness are not considered to be required for the reference product, the same is considered for the biosimilar product.

V.3. Summary of risk minimisation measures

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Infectious endophthalmitis	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, 4.8, 6.6 SmPC section 6.6 where advice is given on how to administer an IVT injection and information for physicians and patients on how to manage this event. PL sections 2, 3 and 4. Pack size: one vial or PFS for single use only Legal status: Prescription only medicine Additional risk minimisation measures: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up checklist Additional pharmacovigilance activities: None
Intraocular inflammation	Routine risk minimisation measures: SmPC sections 4.3 and 4.4. PL sections 2 and 4. Pack size: one vial or PFS for single use only Legal status: Prescription only medicine Additional risk minimisation measures: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Retinal detachment and retinal tear	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PL sections 2 and 4. Pack size: one vial or PFS for single use only Legal status: Prescription only medicine Additional risk minimisation measures: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Intraocular pressure increase	Routine risk minimisation measures: SmPC sections 4.4, 4.8 and 4.9. SmPC section 4.4 where advice is given on monitoring IOP and the perfusion of the optic nerve head. PL sections 2 and 4. Pack size: one vial or PFS for single use only Legal status: Prescription only medicine Additional risk minimisation measures: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR)	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 Ranivisio (ranibizumab)

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

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

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

I. The medicine and what it is used for

Ranivisio is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (nAMD), 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), and proliferative diabetic retinopathy (PDR). It contains ranibizumab as the active substance and it is given by intravitreal injection. It must be administered by a qualified ophthalmologist experienced in intravitreal injections.

Further information about the evaluation of Ranivisio's benefits can be found in Ranivisio's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

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

Important risks of Ranivisio, together with measures to minimise such risks and the proposed studies for learning more about Ranivisio'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 Ranivisio, 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*.

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

II.A List of important risks and missing information

Important risks of Ranivisio 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 Ranivisio. 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

II.B Summary of important risks

Important identified risk Infectious endophthalmitis	
Evidence for linking the risk to the medicine	Infectious endophthalmitis can possibly lead to a loss of vision and sometimes even to the loss of the eye itself.
Risk factors and risk groups	Ranibizumab 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: SmPC Sections 4.2, 4.3, 4.4, 4.8, 6.6. SmPC section 6.6 where advice is given on how to administer an IVT injection and information for physicians and patients on how to manage this event PL Sections 2, 3, 4 Pack size: one vial or PFS for single use only Legal status: Prescription only medicine

	Additional risk minimisation measures: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR)

Important identified risk Intraocular inflammation	
Evidence for linking the risk to the medicine	Intraocular inflammation can possibly lead to a loss of vision and sometimes even to the loss of the eye itself.
Risk factors and risk groups	Proper aseptic injection techniques must always be used when administering ranibizumab and injection must not be given to patients with active severe intraocular inflammation.
Risk minimisation measures	Routine risk minimisation: SmPC Sections 4.3, 4.4 PL Sections 2, 4 Pack size: one vial or PFS for single use only Legal status: Prescription only medicine Additional routine risk minimisation measures: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR)

Important identified risk 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.
Risk factors and risk groups	The following conditions might increase the risk for retinal detachment: previous retinal detachment or retinal tear, eye tumours, inflammation in the choroid or the retina, eye injury, or severe high blood pressure.
Risk minimisation measures	Routine risk minimisation: SmPC Sections 4.4, 4.8 PL Sections 2, 4 Pack size: one vial or PFS for single use only Legal status: Prescription only medicine Additional routine risk minimisation measures: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR)

Important identified risk Intraocular pressure increase	
Evidence for linking the risk to the medicine	The injection of a volume of 50 µL of ranibizumab may lead to an increase in IOP.

Risk factors and risk groups	Pre-existing high IOP is a risk factor. Ranibizumab should not be administered in the event of an IOP of ≥30 mmHg.
Risk minimisation measures	Routine risk minimisation: SmPC Sections 4.4, 4.8, 4.9 SmPC Section 4.4 where advice is given on monitoring IOP and the perfusion of the optic nerve head. PL Section 2, 4 Pack size: one vial or PFS for single use only Legal status: Prescription only medicine Additional risk minimisation measures: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR)

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 Ranivisio.

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

There are no studies required for Ranivisio.

Part VII: Annexes

Note: For annexes 4 and 6, materials are kept as similar as possible with the reference product in order to deliver a consistent message.

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Annex 4 – Specific adverse drug reaction follow-up forms

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Follow-up form

Targeted Follow-up Checklist: Ranibizumab Endophthalmitis (Version 1/ Jun-2021)

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
- Is the patient immunocompromised?
  ☐ Yes ☐ No ☐ Unknown
  - If yes, please describe

Annex 6 – Details of proposed additional risk minimisation activities

Draft key messages of the additional risk minimisation measures

Prior to the launch of ranibizumab biosimilar in each Member State the Marketing Authorisation Holder (MAH) shall agree on the final educational material with the National Competent Authority.

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

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

The patient information pack:

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 will be provided to all ophthalmology clinics where ranibizumab is expected to be used for the treatment of adult patients, thus the physicians can distribute it further to their patients.

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

- Patient information leaflet
- How to prepare for ranibizumab treatment
- What are the steps following treatment with ranibizumab
- 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 programme 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 audio format) will be developed in accordance with the reference product. The booklets will be 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), DME, RVO, and PDR
- 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 will be 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 for the treatment of adult patients.