# EU Risk Management Plan for Lytenava (Bevacizumab gamma)

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# Table of contents

**Table of contents** ..... **2**
**List of Tables** ..... **3**
**List of Abbreviations** ..... **4**
**Part I: Product Overview** ..... **5**
**Part II: Module SI - Epidemiology of the indication(s) and target population(s)** ..... **7**
**Part II: Module SII - Non-clinical part of the safety specification** ..... **16**
**Part II: Module SIII - Clinical trial exposure** ..... **17**
**Part II: Module SIV - Populations not studied in clinical trials** ..... **20**
SIV.1 Exclusion criteria in pivotal clinical studies within the development programme ..... 20
SIV.2 Limitations to detect adverse reactions in clinical trial development programmes ..... 21
SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes ..... 21
**Part II: Module SV - Post-authorisation experience** ..... **23**
SV.1 Post-authorisation exposure ..... 23
**Part II: Module SVI - Additional EU requirements for the safety specification** ..... **23**
**Part II: Module SVII - Identified and potential risks** ..... **24**
SVII.1 Identification of safety concerns in the initial RMP submission ..... 24
SVII.2 New safety concerns and reclassification with a submission of an updated RMP ..... 28
SVII.3 Details of important identified risks, important potential risks, and missing information ..... 28
**Part II: Module SVIII – Summary of the safety concerns** ..... **34**
**Part III: Pharmacovigilance Plan (including post-authorisation safety studies)** ..... **34**
III.1 Routine pharmacovigilance activities ..... 34
III.2 Additional pharmacovigilance activities ..... 35
III.3 Summary Table of additional Pharmacovigilance activities ..... 35
**Part IV: Plans for post-authorisation efficacy studies** ..... **35**
**Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)** ..... **36**
V.1. Routine Risk Minimisation Measures ..... 36
V.2. Additional Risk Minimisation Measures ..... 39
V.3 Summary of risk minimisation measures ..... 41
**Part VI: Summary of the risk management plan** ..... **47**
II.A List of important risks and missing information ..... 49
II.B Summary of important risks ..... 49
II.C Post-authorisation development plan ..... 54
II.C.1 Studies which are conditions of the marketing authorisation ..... 54
II.C.2 Other studies in post-authorisation development plan ..... 54

**Part VII: Annexes ..... 55**
Annex 1. EudraVigilance Interface .....
Annex 2. Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme .....
Annex 3. Protocols for proposed, on-going and completed studies in the pharmacovigilance plan
Annex 4. Specific adverse drug reaction follow-up forms ..... 56
Endophthalmitis: follow-up questionnaire ..... 56
Thromboembolic events in the eye(s): follow-up questionnaire ..... 72
Annex 5. Protocols for proposed and on-going studies in RMP part IV .....
Annex 6. Details of proposed additional risk minimisation activities (if applicable) ..... 65
Annex 7. Other supporting data (including referenced material) .....
Annex 8. Summary of changes to the risk management plan over time .....

# List of Tables

Table 1: Product Overview ..... 5
Table 2. Description of the European Eye Epidemiology Consortium Studies Included in the Meta-Analysis (Colijn 2017) ..... 8
Table 3. Random-effects meta-analysis and meta-regression of AMD prevalence and incidence (Li 2020) ..... 10
Table 4. European countries where off-label use of bevacizumab is common for ophthalmic conditions ..... 14
Table 5: Duration of exposure to in subjects treated with bevacizumab gamma (ONS-5010) ..... 18
Table 6: Extent of exposure by age group and gender for subjects with nAMD, DME and BRVO ..... 18
Table 7: Extent of exposure by age group and gender for subjects with nAMD ..... 19
Table 8: Ethnic origin in subjects treated with bevacizumab gamma (ONS-5010) ..... 19
Table 9 Exclusion criteria in pivotal clinical studies within the development programme ..... 20
Table 10: Exposure of special populations included or not in clinical trial development programmes ..... 21
Table 11: Summary of safety concerns ..... 34
Table 12: Description of routine risk minimisation measures by safety concern ..... 36
Table 13: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern ..... 41

# List of Abbreviations

| | |
|---|---|
| ADA | Anti-drug antibodies |
| AMD | Age-related macular degeneration |
| AR | Adverse reaction |
| ATE | Arterial thromboembolic events |
| BRVO | Branched retinal vein occlusion |
| CATT | Comparison of AMD Treatment Trials |
| CNV | Choroidal neovascularization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DME | Diabetic macular oedema |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| ERG | Electroretinography |
| GHS | Gutenberg Health Study |
| GLP | Good Laboratory Practice |
| IOI | Intraocular inflammation |
| IOP | Intraocular pressure increase |
| LUCAS | Lucentis Compared to Avastin Study |
| NHP | Non-human primate |
| nAMD | Neovascular age-related macular degeneration |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PED | Pigment epithelial detachment |
| PL | Patient Information Leaflet |
| RMP | Risk management plan |
| RPE | Retinal pigment epithelium |
| SD | Standard deviation |
| SmPC | Summary of product characteristics |
| VEGF | Vascular endothelial growth factor |

# Part I: Product Overview

**Table 1: Product Overview**

| | |
|---|---|
| **Active substance(s)**<br><br>**(INN or common name)** | Bevacizumab gamma (ONS-5010) |
| **Pharmacotherapeutic group(s) (ATC Code)** | Antineovascularisation agents (S01LA08) |
| **Marketing Authorisation Applicant** | Outlook Therapeutics Limited |
| **Medicinal products to which this RMP refers** | One |
| **Invented name(s) in the European Economic Area (EEA)** | Lytenava |
| **Marketing authorisation procedure** | Centralised |
| **Brief description of the product** | **Chemical class:** IgG1 monoclonal antibody specific for VEGF binding |
| | **Summary of mode of action:** Bevacizumab gamma prevents the binding of VEGF to the receptors Flt-1 and KDR and thus inhibits VEGF/VEGFR mediated endothelial cell proliferation and angiogenesis. Inhibition of angiogenesis works to block the growth of abnormal blood vessels in the back of the eye. |
| | **Important information about its composition:** Bevacizumab gamma is a recombinant humanised monoclonal antibody produced by DNA technology in Chinese Hamster Ovary cells. |
| **Hyperlink to the Product Information** | ema.europa.eu/medicines/human/EPAR/lytenava |
| **Indication(s) in the EEA** | **Current:**<br><br>Lytenava is indicated in adults for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD) |
| | **Proposed (if applicable):**<br><br>Not applicable |
| **Dosage in the EEA** | **Current:**<br><br>The recommended dose for Lytenava in adults is 1.25 mg administered as a single intravitreal injection every 4 weeks (monthly). This corresponds to an injection volume of 0.05 mL. |
| | **Proposed (if applicable):**<br><br>Not applicable |

| | |
|---|---|
| **Pharmaceutical form(s) and strengths** | **Current (if applicable):**<br>Solution for injection: 25 mg/mL solution for intravitreal injection in a single-dose glass vial. Each vial contains 7.5 mg of bevacizumab gamma in 0.3 mL solution, which is adequate to deliver 0.05 mL (equivalent to 1.25 mg) of bevacizumab gamma). |
| | **Proposed (if applicable):**<br>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)

Lytenava (bevacizumab gamma) is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD)

Advanced or late AMD is classified into 2 clinical subtypes: the non-neovascular (atrophic) or dry form, and the neovascular (exudative) or wet form (Ferris 1984, Lim 2012, Miller 2013). Neovascular AMD (nAMD) is characterised by the growth of abnormal new blood vessels (neovascularisation) under the retinal pigment epithelium (RPE) or subretinal space from the subjacent choroid, termed choroidal neovascularisation (CNV) (Ferris 1984). Bleeding and fluid leakage from these new blood vessels can then cause the macula to bulge or lift up from its normally flat position, thus distorting or destroying central vision (Chen 2021). Under these circumstances, vision loss may be rapid and severe. VEGF is elevated in patients with nAMD and is thought to play a key role in the neovascularistion process (Spilsbury 2000).

Incidence and Prevalence:

Globally, the projected number of people with AMD in 2020 is 196 million, increasing to 288 million in 2040 (Wong 2014). Approximately 67 million people in the EU are estimated to be affected by AMD and, due to population ageing, this number is expected to increase by 15% until 2050 (Li et al. 2019).

To estimate the prevalence of early and late AMD in Europe, Colijn et al performed a meta-analysis based on summary data of population-based cohort studies from the European Eye Epidemiology Consortium (Colijn 2017). Overall, a total of 42,080 individuals participating in 14 population-based cohorts from 10 countries in Europe were included in this analysis. The prevalence of all age groups together varied per study between 2.3% and 16.8% for early AMD and between 0.2% and 5.6% for late AMD (Table 2).

**Table 2. Description of the European Eye Epidemiology Consortium Studies Included in the Meta-Analysis (Colijn 2017)**

| Region | | Study | Data Collection Period | Total Participants (n) | Age Range (yrs) | Median Age (yrs) | Male Gender (%) | European Ethnicity (%) | Crude Prevalence of Early AMD (%) | Crude Prevalence of Late AMD (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| North | United Kingdom | EPIC | 2004–2011 | 5344 | 45–85+ | 60–64 | 43.1 | 99.7 | – | 0.5 |
| | Norway | Tromsø | 2007–2008 | 2631 | 65–85+ | 65–69 | 42.5 | 91 | – | 3.5 |
| West | France | ALIENOR-3C | 2006–2008 | 879 | 70–85+ | 75–79 | 37.7 | – | 16.8 | 5.6 |
| | Germany | GHS | 2007–2012 | 3839 | 40–74 | 50–54 | 50.2 | – | 2.3 | 0.2 |
| | Netherlands | RS-I | 1990–1993 | 6419 | 55–85+ | 60–64 | 40.7 | 98.9 | 7.5 | 1.7 |
| | Netherlands | RS-II | 2000–2002 | 2545 | 55–85+ | 55–59 | 45.4 | 97.8 | 6 | 0.7 |
| | Netherlands | RS-III | 2005–2008 | 3449 | 45–85+ | 55–59 | 43.4 | 96.4 | 4.6 | 0.4 |
| | France | Montrachet-3C | 2009–2013 | 1069 | 75–85+ | 80–84 | 37 | 100 | 9.2 | 2.2 |
| | France | POLA | 1995–1997 | 2196 | 60–85+ | 65–69 | 43.5 | – | 8.7 | 1.9 |
| South | Portugal | Lousa | 2012–2013 | 3021 | 55–85+ | 60–64 | 43.9 | 99.3 | 15.4 | 1.3 |
| | Portugal | Mira | 2009–2011 | 2975 | 55–85+ | 65–69 | 43.4 | 99.7 | 6.9 | 0.7 |
| | Thessaloniki | Thessaloniki Eye Study | 2000–2005 | 2107 | 60–85+ | 65–69 | 55.6 | 97.7 | – | 2.7 |
| | Italy | PAMDI | 2005–2006 | 853 | 60–85+ | 65–69 | 45.8 | 100 | 13.5 | 2.1 |
| Multiple | | EUREYE | 2000–2002 | 4753 | 65–85+ | 65–69 | 44.8 | – | 12.6 | 3.3 |

ALIENOR = Antioxydants, Lipids Essentials, Nutrition et maladies OculaiRes Study; AMD = age-related macular degeneration; EPIC = European Prospective Investigation into Cancer; EUREYE = European Eye Study; GHS = Gutenberg Health Study; PAMDI = Prevalence of Age-Related Macular Degeneration in Italy; POLA = Pathologies Oculaires Liées à l'Age Study; RS = Rotterdam Study; – = data not available.

Applying a random-effects model for each analysis, prevalence of early AMD was shown to increase from 3.5% in those aged 55 - 59 years to 17.6% in those aged ≥85 years (Colijn 2017); for late AMD these figures were 0.1% and 9.8%, respectively. The prevalence of late AMD rose from virtually zero in the youngest age group to 9.8% for those in the highest age group. For late AMD, a trend of decreasing prevalence was observed for the higher age categories after 2006. With respect to regional differences across Europe, late AMD had the highest prevalence in the North (4.2%) compared to the West (3.1%) and South (3.1%). Despite a decreasing prevalence, projections of AMD showed an almost doubling of affected persons. By 2040, the number of individuals in Europe with early AMD will range between 14.9 and 21.5 million, and for late AMD between 3.9 and 4.8 million.

In a meta-analysis, the prevalence and incidence of AMD in Europe was estimated based on studies conducted in Germany, France, Italy, Spain, and the UK (Li 2020). Overall, 26 studies were considered – 22 prevalence studies including data from 55,323 individuals (mean age range 60-81 years) and 4 incidence studies with pooled data from 7,223 study participants (Li 2020). Pooled prevalence for any late AMD ranged from 0.3% to 6.4% and prevalence of nAMD was estimated at 1.4% (Table 3). Regarding future projections, more than 77 million individuals in the EU are estimated to be affected by any AMD as compared with 67 million in the year 2015.

**Table 3. Random-effects meta-analysis and meta-regression of AMD prevalence and incidence (Li 2020)**

| | | N | Early/intermediate AMD | N | Any late AMD | N | nAMD | N | GA |
|---|---|---|---|---|---|---|---|---|---|
| *Meta-analysis: Pooled prevalence, 60+ (%, 95% CI)* | | | | | | | | | |
| Total | | 19 | 25.3 (18.6 to 34.4) | 22 | 2.4 (1.8 to 3.3) | 15 | 1.4 (1.0 to 1.9) | 15 | 1.0 (0.7 to 1.5) |
| P (Q-het) | | | <0.01 | | <0.01 | | <0.01 | | <0.01 |
| $I^2$ (%) | | | 100 | | 97 | | 94 | | 93 |
| *Meta-regression by age: Pooled prevalence of AMD (%), 95% CI* | | | | | | | | | |
| ≤64 years | | 6 | 9.3 (4.4 to 18.5) | 8 | 0.3 (0.1 to 0.5) | 5 | 0.1 (0.1 to 0.3) | 5 | 0.1 (0.0 to 0.2) |
| 65–74 years | | 11 | 18.5 (11.3 to 28.9) | 15 | 1.5 (1.1 to 1.9) | 11 | 0.8 (0.6 to 1.0) | 11 | 0.6 (0.4 to 0.9) |
| ≥75 years | | 10 | 26.9 (16.7 to 40.3) | 14 | 6.4 (5.2 to 8.0) | 11 | 3.3 (2.5 to 4.2) | 11 | 3.2 (2.3 to 4.3) |
| P (Q-het) | | | <0.01 | | <0.01 | | <0.01 | | <0.01 |
| P (Q-mod) | | | 0.04 | | <0.01 | | <0.01 | | <0.01 |
| $I^2$ (%) | | | 99.2 | | 82.0 | | 0 | | 0 |
| Pseudo-$R^2$ (%) | | | 18.4 | | 79.8 | | 81.7 | | 64.6 |
| *Meta-regression by country and age combined: Pooled prevalence of AMD (%), 95% CI* | | | | | | | | | |
| Germany | ≤64 | | 13.2 (8.7 to 19.6) | | 0.4 (0.2 to 0.8) | | 0.1 (0.0 to 0.3) | | 0.1 (0.0 to 0.2) |
| | 65 to 75 | | 22.9 (16.7 to 30.7) | | 1.5 (1.1 to 2.1) | | 0.3 (0.1 to 0.8) | | 0.3 (0.1 to 0.8) |
| | ≥75 | | 34.2 (24.6 to 45.3) | | 6.7 (5.0 to 8.9) | | 1.1 (0.4 to 3.3) | | 1.2 (0.4 to 3.3) |
| France | ≤64 | | 8.8 (3.5 to 20.3) | | 0.4 (0.2 to 0.8) | | 0.4 (0.2 to 0.8) | | 0.2 (0.1 to 0.4) |
| | 65 to 75 | | 15.8 (6.9 to 32.2) | | 1.4 (0.9 to 2.1) | | 1.4 (0.9 to 2.1) | | 0.7 (0.4 to 1.1) |
| | ≥75 | | 24.7 (12.4 to 43.2) | | 6.0 (4.1 to 8.7) | | 6.0 (4.1 to 8.7) | | 2.8 (1.8 to 4.3) |
| UK | ≤64 | | 34.1 (19.9 to 52.0) | | 0.5 (0.3 to 1.0) | | 0.3 (0.1 to 0.6) | | 0.2 (0.1 to 0.6) |
| | 65 to 75 | | 50.3 (35.4 to 65.2) | | 1.9 (1.4 to 2.5) | | 0.8 (0.6 to 1.0) | | 1.0 (0.8 to 1.3) |
| | ≥75 | | 63.9 (48.9 to 76.6) | | 8.1 (6.3 to 10.3) | | 3.2 (2.5 to 4.1) | | 4.3 (3.4 to 5.3) |
| Italy | ≤64 | | – | | 0.6 (0.3 to 1.1) | | – | | – |
| | 65 to 75 | | – | | 2.1 (1.4 to 3.2) | | – | | – |
| | ≥75 | | – | | 9.1 (6.2 to 13.1) | | – | | – |
| Spain | ≤64 | | 4.2 (2.0 to 8.4) | | 0.4 (0.2 to 0.7) | | 0.3 (0.1 to 0.6) | | 0.2 (0.1 to 0.4) |
| | 65 to 75 | | 7.8 (4.3 to 13.7) | | 1.3 (0.9 to 1.8) | | 0.7 (0.5 to 1.0) | | 0.7 (0.5 to 1.0) |
| | ≥75 | | 12.9 (7.3 to 21.7) | | 5.8 (4.3 to 7.7) | | 3.0 (2.2 to 4.1) | | 2.8 (2.1 to 3.9) |
| p (Q-het) | | | <0.01 | | 0.20 | | 0.62 | | 0.57 |
| P (Q-mod) | | | <0.01 | | <0.01 | | <0.01 | | <0.01 |
| $I^2$ (%) | | | 95.1 | | 20.3 | | 0 | | 0 |
| Pseudo-$R^2$ (%) | | | 84.9 | | 97.8 | | 100 | | 100 |
| *Pooled annual incidence of any late AMD by age (per 1000), 95% CI* | | | | | | | | | |
| Total | | | – | 3 | 1.4 (0.8 to 2.6) | | – | | – |
| P (Q-het) | | | | | <0.01 | | | | |
| $I^2$ (%) | | | – | | 57.3 | | – | | – |
| *Meta-regression by age: Pooled annual incidence of any late AMD (per 1000), 95% CI* | | | | | | | | | |
| <70 years | | | – | 3 | 0.5 (0.1 to 2.7) | | – | | – |
| ≥70 years | | | – | 4 | 6.7 (3.2 to 14.1) | | – | | – |
| P (Q-het) | | | | | 0.20 | | | | |
| P (Q-mod) | | | | | <0.01 | | | | |
| $I^2$ (%) | | | | | 31.6 | | | | |
| Pseudo-$R^2$ (%) | | | | | 79.4 | | | | |

AMD, age-related macular degeneration; GA, geographic atrophy;
$I^2$, measure of heterogeneity; n, number of studies with available data; nAMD, neovascular AMD; pseudo-$R^2$, coefficient of determination in regression model; Q-het, Cochran's Q-test for heterogeneity; Q-mod, Q test for moderators.

In 2018, annual incidence was 0.149% and prevalence was 1.062% in France for a population 50 years of age or older (Creuzot-Garcher 2022). Incidence was stable over the 10-year period. Annual incidence increased with age (0.223%, 0.380%, and 0.603% in those 60 years of age or older, 70 years of age or older, and 80 years of age or older, respectively), with similar trends for prevalence.

Across Scandinavia in 2013, a total of 187,000 persons aged ⩾65 years in Scandinavia were affected by late AMD: 47,000 in Denmark, 43,000 in Norway and 97 000 in Sweden (Lindekleiv 2013). Owing to an ageing population, the number of persons affected by late AMD are expected to increase by 75% to 328,000 in 2040 in Scandinavia.

With respect to nAMD, projections for Denmark reported the number of patients to increase from 30,000 in 2016 to 33,000 in 2020, to 58,000 in 2040, and to 72,000 in 2060 (Sedeh 2017).

In Ireland, the estimated overall prevalence of any AMD is 7.2% in the population aged 50 years or older, while the estimated prevalence of early AMD is 6.6% and late AMD is 0.6% (Akuffo 2015).

In Germany, the cumulative incidence of AMD over 5 years is reported to be 2.0%, with 18.1% of patients with AMD showing progression in at least one eye in this time frame (Korb 2022).

In Portugal, the overall prevalence of early and late AMD has been calculated to be 15.53% (95% CI 14.25-16.88) and 0.67% (95% CI 0.41-1.04), respectively, with the highest prevalence of advanced AMD among those aged ⩾75 years (Cachulo 2015).

In Spain, the overall prevalence of AMD is reported to be 7.6%, with a prevalence for early, intermediate and advanced AMD as 2.9%, 2.7%, and 2.0%, respectively (Zapata 2021).

Demographics of AMD patients

The prevalence and incidence of AMD increases with age. In age groups ≤64 years, 65-74 years, and ≥75 years, prevalence is estimated to be 0.3%, 1.5% and 6.4%, respectively, for any late AMD, and 0.1%, 0.8% and 3.3%, respectively, for nAMD, based on a meta-analysis performed using data from 22 European studies (Li 2020). In the Rotterdam Study, the overall 2-year cumulative incidence of AMD was reported to be 0.2%, increasing to 1.8% in subjects of 85 years and older (Klaver 2001).

No significant gender effect has been noted in the overall prevalence of AMD in several meta-analyses (Colijn 2017, Li 2020, Wong 2014). For the age category ≥85 years, a trend of higher prevalence of early and late AMD in women compared to men has been reported (Colijn 2017). Regarding nAMD, a higher risk has been reported in women compared to men (Rudnicka 2012, Zhou 2021).

Race or ethnicity has been reported to be a predictor for AMD, with a higher prevalence observed in white populations. In a meta-analysis, pooled prevalence of AMD was calculated based on ethnically diverse population-based studies and confirmed that prevalence was greatest among those individuals of European descent at 12.3–30% with increasing age (Wong 2014). While a difference in prevalence of nAMD based on ethnicities was not seen in the meta-analysis performed by Wong et al, other analyses have demonstrated higher prevalence and incidence in white nAMD patients than in Hispanic, Asian, and black patients (Vanderbeek 2011).

Racial/ethnic differences in AMD prevalence have been attributed to variations in pigmentation. Eyes with more pigmentation are thought to be protected against development of neovascular AMD (Frank 2000, Weiter 1985). However, the association of iris color with AMD has not been consistently demonstrated (Sun 2014).

Risk Factors for AMD

The main risk factor for AMD is age (Stahl 2020). Neovascular AMD generally onsets in individuals older than 50 years of age. It is suggested that 10% of individuals aged 65 to 74 years, and 30% of those aged 75 to 85 years, show signs of AMD.

Other observed risk factors include cigarette smoking, nutritional factors, cardiovascular diseases, and genetic predisposition.

In a systematic review with 17,236 cases of late AMD, increasing age, current cigarette smoking, previous cataract surgery, and a family history of AMD showed strong and consistent associations with late AMD (Chakravarthy 2010). Risk factors with moderate and consistent associations were higher body mass index, history of cardiovascular disease, hypertension, and higher plasma fibrinogen.

The genetic risk and lifestyle factors associated with AMD were analysed using cross-sectional data from the European Eye Epidemiology Consortium from 17,174 individuals (Colijn 2021). The complement pathway and ARMS2 were by far the most prominent genetic pathways contributing to late AMD (positive genetic risk score, 90% of patients with late disease), but risk in 3 pathways was most frequent (35% of patients with late disease). Lifestyle, as measured by smoking status and dietary considerations, was a strong determinant of the outcome in each genetic risk category, with an unfavorable lifestyle increasing the risk of late AMD at least 2-fold (Colijn 2021).

The presence of nAMD in one eye is a major risk factor for the development of disease in the fellow eye (Wong 2020). Once advanced AMD occurs in one eye, the risk for developing advanced AMD in the second eye over a 5-year period is 43% (Bressler 2003). In a pooled data analysis of three prospective population-based cohorts including 1490 participants, 9–28% of unilateral any AMD cases progressed to bilateral, and 27–68% of unilateral late AMD cases progressed to bilateral over a 5-year period (Joachim 2017). In addition to age and AMD genetic risk, smoking and early AMD lesion characteristics were associated with increased risk of progression from unilateral to bilateral involvement in 5 years. Specifically regarding nAMD, a further meta-analysis showed that unilateral nAMD developed in the fellow eye in 12.2% of patients by 12 months and in 26.8% by 4 years.

The main existing treatment options:

Intravitreal anti-VEGF therapies are currently the standard of care for treating nAMD. VEGF are angiogenic factors which are found elevated in patients with nAMD and play a key role in the neovascularization process. Anti-VEGF therapies inhibit VEGF signalling pathways and have been shown to halt the growth of neovascular lesions and resolve retinal oedema in patients with nAMD. Available VEGF-inhibitors for the treatment of nAMD include the authorised therapies ranibizumab (Lucentis®), aflibercept (Eylea®), brolucizumab (Beovu®), and faricimab (Vabysmo®), as well as the off-label use of bevacizumab (Avastin®). Before the introduction of effective VEGF therapies, a diagnosis of wet AMD meant certain, irreversible central vision loss (Flores 2021).

In Europe, the opinion for off-label use of Avastin® for AMD is varied across the member states (Bro et al 2020). The US Food & Drug Administration (FDA) is supportive of off-label use of Avastin® for AMD as documented in the Summary document for *FDA Draft Guidance Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application* dated February 2015. The summary states 'the draft guidance will allow for compounding facilities to continue to repackage bevacizumab for ophthalmic use' (ASRS, 2015). The current FDA guidance document *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application* is dated January 2018 (FDA 2018).

A survey performed by the American Society of Retina Specialists (Singh, 2018) included 298 members practicing in Europe and 740 members practicing in the US. In the survey, bevacizumab (Avastin®) was reported as the first-line anti-VEGF agent for wet AMD in 30.9% of members practicing in Europe, and 70.2% of members practicing in the US.

Table 4 demonstrates that bevacizumab is highly used in selected European countries for intravitreal injections, including for treatment of wet AMD.

**Table 4. European countries where off-label use of bevacizumab is common for ophthalmic conditions**

| Country | Share of Bevacizumab Use for Intravitreal Injections |
|---|---|
| Bulgaria | 90% |
| Finland | 80-85% |
| Ireland | 70-80% |
| Netherlands | 70-80% |
| Romania | 95-97% |

(Bro et al 2020)

Multiple studies have proven bevacizumab to have comparable efficacy and safety to the registered anti-VEGF drugs, and there is also evidence that bevacizumab is the most cost-effective drug for wet AMD. The cost of anti-VEGF treatment is not only considered an ophthalmologic issue but also a public health matter (Bro et al 2020).

Older management approaches for AMD include radiation therapy, photocoagulation, or photodynamic therapy. For selected patients for whom VEGF-inhibitors are not recommended, for example in pregnant patients, photodynamic or photocoagulation therapy can be considered (Schmidt-Erfurth 2014). Radiation therapy is generally not recommended, as the delivery method, efficacy and safety results remain controversial (Schmidt-Erfurth 2014).

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

AMD is the leading cause of severe vision loss in people over the age of 65 in Europe, the US, and Australia (Kawasaki 2010, Rein 2009, Smith 2001). Overall, AMD is estimated to account for 8.7% of all blindness worldwide (Wong 2008).

AMD is classified as early, intermediate, and late stages whereas late AMD, is subdivided into two types: dry (atrophic) and neovascular (wet, exudative) AMD (Stahl 2020). Late AMD is much more relevant to vision than early AMD, which is often asymptomatic, or intermediate AMD, which is usually oligosymptomatic. Patients usually present with distortion, blurring or a scotoma (black or grey patch) in their central vision, which is rapid in onset in nAMD and more gradually progressive in dry AMD (Cook 2008).

Although the neovascular form of the disease is only present in about 10% of all AMD cases, it accounted for approximately 90% of the severe vision loss from AMD prior to the introduction of anti-VEGF treatments (Ferris 1984, Sommer 1991, Wong 2008). The natural history of nAMD is well-known, with the damage to the retina resulting in progressive, severe, and irreversible vision loss (Shah 2009, Shah 2007). Without treatment, most affected eyes will have poor central vision (20/200) within 12 months (Blinder 2003) and culminates in a doubling of the visual angle (loss of 15 letters) in the year after initial presentation (Wong 2008). A meta-analysis in over 4,000 patients with untreated nAMD revealed that 21.3% of patients developed severe vision loss at 6 months compared with baseline, increasing to 41.9% by 3 years. At 3 years, 75% of patients were legally blind (Wong 2008).

Important comorbidities:

As nAMD primarily affects an older population, many comorbidities in nAMD patients are conditions that are age-related, such as cardiovascular disease, diabetes and dementia.

Based on data from 38,852 nAMD patients in France, a retrospective, longitudinal population study reported the following ocular and non-ocular comorbidities (Creuzot-Garcher 2022):

Hypertension (69.5%), cataract surgery (47.6%), dry eye disease (30,3%), nonmetastatic cancer (20.4%), ocular hypertension (17.3%), diabetes (12.8%), stroke (11.4%), congestive heart failure (10.4%), myocardial infarction (9.1%), renal disease (7.1%), and dementia (3.9%).

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

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

Repeat-dose toxicity:

For bevacizumab, the most relevant species is the non-human primate (NHP), and, therefore, the Good Laboratory Practice (GLP) repeat dose toxicity of bevacizumab gamma (the intravenous dosage form of ONS-5010) was evaluated in cynomolgus monkeys. The choice of intravenous (IV) administration for this study was to provide comparative data between the intravenous bevacizumab gamma (ONS-5010) formulation to intravenous bevacizumab (Avastin), rather than to demonstrate local tolerance and toxicity using intravitreal administration.

In a GLP 4-week toxicity study in cynomolgus monkeys (Study HUD0445), IV administration of 50 mg/kg bevacizumab gamma or 50 mg/kg Avastin twice weekly was associated with physeal dysplasia of the distal femur in males that was similar between the 2 treatment groups and similar to that previously reported in cynomolgus monkeys administered with Avastin (Ryan 1999).

The bevacizumab maximum concentration ($C_{max}$) and area under the serum concentration-time curve estimated up to 48 hours post-dose ($AUC_{48}$) values were lower on Day 1 for bevacizumab gamma than the corresponding values for Avastin but were higher on Day 25. There were generally no differences in the $C_{max}$ values between males and females following administration of either bevacizumab gamma or Avastin; however, the $AUC_{48}$ values in females tended to be slightly higher than those in males.

Several *in vivo* studies have evaluated the toxicity of bevacizumab administered as a single or repeat intravitreal injections in rodents, rabbits, and monkeys. No ocular toxicity at 2.5 mg/eye was observed in rats whereas increased photoreceptor apoptotic activity was observed with a single-dose of ≥ 1.25 mg/eye or 3 monthly injections of 0.625 mg/eye bevacizumab in rabbits. In a single-dose intravitreal toxicity study of bevacizumab in monkeys, no ocular effects were observed at 6.25 mg/eye and ocular effects at 12.5 mg/eye were limited to transient reductions in scotopic electroretinography (ERG) responses.

Relevance to human use:

Although no intravitreal administration has been investigated in non-clinical species with bevacizumab gamma, this has been evaluated in clinical safety and efficacy studies which support the tolerable and effective administration to human vitreous humour.

As with all therapeutic proteins, there is a potential for immunogenicity with bevacizumab gamma. Anti-drug antibodies (ADAs) are indicators of an immune response to the administered therapeutic protein, which for intravitreal injection drugs could potentially result in intraocular inflammation (IOI). Incidence of ADA induction/boosting in 14 subjects across studies ONS-5010-001/ONS-5010-002 was negligible.

Reproductive/developmental toxicity:

Reproductive and developmental toxicity studies with bevacizumab gamma have not been conducted, this is based upon the following justification: 1) a target population of at least 50 years of age that would include primarily postmenopausal women; 2) low systemic exposure following intravitreal administration of bevacizumab gamma; 3) the documented adverse reproductive and developmental effects of VEGF-inhibitors as a class; and 4) the occurrence of reversible effects on female reproductive organs and the lack of effects on male reproductive organs following IV administration of bevacizumab in monkeys at doses at least 500 times the intended clinical dose of bevacizumab gamma (on a mg/kg basis). Since

the reproductive effects of bevacizumab have already been studied and risks have already been identified, the labelling for warnings and precautions are already established.

Pregnant rabbits dosed with 10 mg/kg bevacizumab (approximately 500 times the intended clinical dose of bevacizumab gamma on a mg/kg basis) every 3 days during the period of organogenesis (gestation days 6-18) exhibited de/creases in maternal and foetal body weights and an increased number of foetal resorptions, foetal malformation or alterations, skeletal deformities, and teratogenic effects.

Relevance to human use:

VEGF is a major angiogenic factor involved in the formation of new blood vessels during embryonic and foetal development and placentation. VEGF inhibition has been shown to affect follicular development, corpus luteum function, and fertility. The pharmacological inhibition of angiogenesis by bevacizumab gamma is generally expected to have adverse consequences on the female reproductive cycle, since angiogenesis plays a critical role in ovarian and endometrial function. In general, all anti-angiogenic agents are expected to be teratogenic or otherwise harmful for the foetus and are thus not recommended for use during pregnancy (Avastin 2015, Lambertini 2015, Lucentis 2016).

General safety pharmacology:

In compliance with International Council for Harmonisation (ICH) S6 (R1) guidance, safety pharmacological endpoints were integrated in the GLP four-week repeat dose cynomolgus monkey study (Study HUD0445). Bevacizumab gamma did not induce any changes to heart rate, blood pressure and electrocardiogram endpoints. These findings were comparable between Avastin and control-dosed groups.

Relevance to human use:

In patients, the systemic exposure to bevacizumab gamma via intravitreal injections is low. No adverse effects on general safety pharmacology endpoints were observed in the non-clinical program up to the highest doses via the intravenous route. Bevacizumab gamma was generally well tolerated by patients, with no systemic toxicities observed for any system organ class.

# Part II: Module SIII - Clinical trial exposure

Across the clinical development program, bevacizumab gamma (ONS-5010) has been evaluated in one pivotal Phase 3 study (ONS-5010-002), one supportive Phase 3 study (ONS-5010-001), and one Phase 3 safety study (ONS-5010-003). One safety study ONS-5010-007 is currently ongoing. Pooled safety data is available for the Phase 3 studies: ONS-5010-001, ONS-5010-002 and ONS-5010-003.

For the 341 subjects receiving bevacizumab gamma in the Phase 3 studies, the majority (61.3%) had a diagnosis of nAMD in the study eye at baseline, with 31.7%% and 7.0% of the subjects overall having a diagnosis of diabetic macular oedema (DME) and branched retinal vein occlusion (BRVO), respectively. Note that ONS-5010-001 and ONS 5010-002 were limited to subjects with nAMD; ONS 5010 003 included subjects with nAMD, DME, and BRVO.

All subjects in the Phase 3 studies ONS-5010-001 and ONS-5010-002 received 1.25 mg of bevacizumab gamma every month via intravitreal injection. In the ONS-5010-001 and ONS-5010-002 studies, where the expected treatment duration was up to 12 months, the mean (SD) duration of bevacizumab gamma exposure in the combined studies was 335.0 (78.36) days. In ONS-5010-003, where the treatment duration was up to 3 months and all subjects received bevacizumab gamma, the mean (SD) duration of exposure was 88.6 (8.41) days.

For the Phase 3 studies (ONS-5010-001, ONS-5010-002 and ONS-5010-003), exposure by duration is presented in the table below.

**Table 5: Duration of exposure to in subjects treated with bevacizumab gamma (ONS-5010)**

| Duration of exposure (Given as number of doses / injections in a monthly interval | ONS-5010-001 and ONS-5010-002 Number of patients (%)[2] | ONS-5010-003 Number of patients (%)[2] |
|---|---|---|
| Any exposure | 144 (100.0) | 197 (100.0) |
| 1 dose | 144 (100.0) | 197 (100.0) |
| 2 doses | 138 (100.0) | 195 (100.0) |
| 3 doses | 134 (100.0) | 192 (100.0) |
| 4 doses | 135 (100.0) | 0 |
| 5 doses | 131 (100.0) | 0 |
| 6 doses | 130 (100.0) | 0 |
| 7 doses | 131 (100.0) | 0 |
| 8 doses | 124 ( 99.2) | 0 |
| 9 doses | 125 (100.0) | 0 |
| 10 doses | 121 (100.0) | 0 |
| 11 doses | 123 (100.0) | 0 |
| 12 doses | 125 (100.0) | 0 |

[1.] The denominator used to calculate the percentage of subjects dosed is the number of subjects who had a visit assessment (N).
[2.] Patients were administered monthly intravitreal injections of 1.25 mg of ONS-5010 in the study eye

Across the Phase 3 studies, 58.4% of subjects were female and 41.6% were male.

Only adult patients were included in the Phase 3 studies. The mean (standard deviation) age at time of screening was 71.5 (13.09) years (range: 30 to 97 years). Of 341 subjects with nAMD, DME, and BRVO, 238 (69.8%) were ≥65 years (Table 6). Overall, 209 of 341 (61.3%) subjects exposed to bevacizumab gamma were enrolled with nAMD. These 209 subjects had an age range of 49-97 years, with 192 of 209 (91.9%) subjects being ≥65 years and only 1 subject <50 years. The distribution of males and females over age groups was similar for subjects with nAMD (Table 7).

**Table 6: Extent of exposure by age group and gender for subjects with nAMD, DME and BRVO**

| Age group | M | | F | | Total | |
|---|---|---|---|---|---|---|
| | Patients n (%) | Person time years | Patients n (%) | Person time years | Patients n (%) | Person time years |
| Adults <65 years | 51 (35.9) | 13 | 52 (26.1) | 17 | 103 (30.2) | 30 |
| Elderly people | | | | | | |
| 65-74 years | 33 (23.2) | 17 | 45 (22.6) | 26 | 78 (22.9) | 43 |
| 75-84 years | 37 (26.1) | 26 | 63 (31.7) | 40 | 100 (29.3) | 66 |
| 85+ years | 21 (14.8) | 16 | 39 (19.6) | 25 | 60 (17.6) | 41 |
| Total | 142 (100.0) | 72 | 199 (100.0) | 108 | 341 (100.0) | 180 |

**Table 7: Extent of exposure by age group and gender for subjects with nAMD**

| Age group | M | | F | | Total | |
|---|---|---|---|---|---|---|
| | Patients n (%) | Person time years | Patients n (%) | Person time years | Patients n (%) | Person time years |
| Adults <65 years | 6 (8.0) | 2 | 11 (8.2) | 6 | 17 (8.1) | 9 |
| Elderly people | | | | | | |
| 65-74 years | 17 (22.7) | 13 | 31 (23.1) | 22 | 48 (23.0) | 35 |
| 75-84 years | 31 (41.3) | 25 | 56 (41.8) | 39 | 87 (41.6) | 63 |
| 85+ years | 21 (28.0) | 16 | 36 (26.9) | 24 | 57 (27.3) | 41 |
| Total | 75 (100.0) | 56 | 134 (100.0) | 92 | 209 (100.0) | 148 |

In the pooled safety population across the Phase 3 studies, the majority of subjects receiving bevacizumab gamma were white (314/341 subjects; 92.1%).

**Table 8: Ethnic origin in subjects treated with bevacizumab gamma (ONS-5010)**

| **Ethnic origin** | **Number of patients (%)** | **ONS-5010-001 and ONS-5010-002 Doses per patient** | **ONS-5010-003 Doses per patient** |
|---|---|---|---|
| White | 314 (92.1) | 10.9 | 3.0 |
| Asian | 6 (1.8) | 6.5 | 3.0 |
| Black or African American | 9 (2.6) | 11.0 | 3.0 |
| Native Hawaiian or Pacific Islander | 0 | 0 | 0 |
| American Indian or Alaskan Native | 0 | 0 | 0 |
| Other | 11 (3.2) | 12.0 | 3.0 |
| Missing | 1 (0.3) | 0 | 3.0 |
| Total | 341 (100) | 13.7 | 3.0 |

Bevacizumab gamma has been evaluated in one completed Phase 1 PK study (CHDR1427_ONS-1045-001). A total of 45 subjects were enrolled and received a single intravenous administration of 2.0 mg/kg of ONS-1045, the intravenous formulation of bevacizumab gamma. All subjects were healthy males with a mean (standard deviation) age at time of screening was 25.5 (8.6) years (range: 18 to 55 years).

Finally, bevacizumab gamma is being evaluated in an ongoing Phase 3 safety study (ONS-5010-007). Bevacizumab gamma, manufactured using the proposed commercial process, is supplied in vials (Cohort 1) or pre-filled syringes (Cohort 2). Sixty subjects were enrolled in Cohort 1 and treated with bevacizumab gamma supplied in vials. All Cohort 1 subjects have completed the 3-month follow-up of the study, and no new or adverse safety signals were observed during their participation that would alter the established safety profile for bevacizumab gamma derived from the completed studies.

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

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

**Table 9 Exclusion criteria in pivotal clinical studies within the development programme**

| Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale (if not included in Missing information) |
|---|---|---|---|
| **Exclusion criteria in Pivotal Study ONS-5010-002** | | | |
| Uncontrolled glaucoma | Uncontrolled glaucoma could lead to serious complications, loss of vision, and need for intervention | No | A warning to use Lytenava with caution in patients with poorly controlled glaucoma and to not inject Lytenava if the intraocular pressure is ≥30mmHg is included in the SmPC (Section 4.4) and PL (Section 2).<br>Moreover, a warning is included also in the Patient information pack. |
| Active intraocular inflammation (grade trace or above) in the study eye | Active inflammation has been excluded to minimise the risk for other intraocular complications, including infection, that can result from intravitreal injections | No | Lytenava is contraindicated in patients with ocular or periocular infections (SmPC Sections 4.3 and 4.4 and PL Section 2 and 4).<br>A contraindication alert is included also in the Patient information pack. |
| Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye | Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis have been excluded to reduce the risk for further infection following intravitreal injection. | No | Lytenava is contraindicated in patients with ocular or periocular infections (SmPC Section 4.3 and PL (Section 2).<br>A contraindication alert is included also in the Patient information pack. |
| Pregnant or nursing female patients | Based on the anti-VEGF mechanism of action for bevacizumab gamma, treatment with Lytenava may pose a risk to human embryofoetal development.<br>Since there are no data on whether Lytenava is excreted in human milk, a potential for absorption and harm to a nursing infant cannot be excluded. | No | Guidance on the use of Lytenava in women of child-bearing potential without the use of effective contraception, pregnant women nor in breastfeeding women considering the potential risks to the foetus and nursing infant is provided in the SmPC (Section 4.6) and PIL (Section 2).<br>A warning for the use in case of pregnancy and/or brestfeeding is included also in the Patient information pack. |

| Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale (if not included in Missing information) |
|---|---|---|---|
| | Lytenava should therefore only be used during pregnancy or breastfeeding if the potential benefit justifies the potential risk for the mother and the foetus or breastfed child. | | |
| Known allergy to any component of the study drug or history of allergy to fluorescein, not amenable to treatment | Patients with a known allergy to the active substance or to any of its excipients are thought to be at increased risk of hypersensitivity reactions. | No | Hypersensitivity to the active substance or to any of the excipients is a contraindication for use (SmPC, Section 4.3 and PL Section 2). As further stated in the SmPC, hypersensitivity reactions may manifest as severe intraocular inflammation.<br>A contraindication alert is included also in the Patient information pack. |

## 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
- those caused by prolonged exposure
- those caused by cumulative exposure

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

Exposure of special populations included or not included in the clinical development program is described below.

**Table 10: Exposure of special populations included or not in clinical trial development programmes**

| Type of special population | Exposure |
|---|---|
| Pregnant women | |

| | |
|---|---|
| Breastfeeding women | Pregnant and breastfeeding women were not included in the clinical development program.<br><br>Female patients who were pregnant or planning to get pregnant were not eligible for participation in the studies. Based on the anti-VEGF mechanism of action for bevacizumab gamma, treatment with Lytenava may pose a risk to human embryofoetal development.<br><br>As it is unknown whether bevacizumab gamma is excreted in human milk and therefore risk to a nursing child cannot be excluded, breastfeeding women were not eligible to be included in the studies. |
| Patients with relevant comorbidities:<br>• Patients with hepatic impairment<br>• Patients with renal impairment<br>• Patients with cardiovascular impairment<br>• Immunocompromised patients<br>• Patients with a disease severity different from inclusion criteria in clinical trials | Patients with relevant comorbidities were not explicitly excluded from the clinical development program. However, patients with a history of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicated the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications were excluded. |
| Population with relevant different ethnic origin | The majority of patients enrolled in the clinical development program were Caucasian (92.1%).<br><br>Considering that nAMD is more prevalent in a white population, this appropriately reflects the primary population to be treated. |
| Subpopulations carrying relevant genetic polymorphisms | Not included in the clinical development program. |
| Elderly | nAMD is most common in patients over the age of 50 years. In the Phase 3 studies, the mean age of the patients receiving bevacizumab gamma was 74 years at screening, with 91.9% of nAMD subjects being ≥65 years of age.<br><br>The elderly have therefore been adequately represented in the clinical trials and the age distribution reflects that of nAMD. |

| | |
|---|---|
| Children | Children and adolescents were not included in the study populations.<br><br>Age related macular degeneration is listed in the class waiver published in EMA/498952/2015 Corr, CW/0001/2015 Opinion of the Paediatric Committee on the review of the list of class waivers (see Section 4: "All classes of medicinal products for treatment of age-related macular degeneration and diabetic macular oedema"). It was confirmed by the Agency on 30 September 2020 falls under the scope of this decision. |
| Other | Not applicable. |

# Part II: Module SV - Post-authorisation experience

No post marketing data is available from EU or other regions outside EU for Lytenava, as this RMP is submitted within an initial marketing authorisation application.

Otherwise, off-label use of bevacizumab products (authorised for other indications) is documented in the medical and scientific literature.

Off-label use of bevacizumab (Avastin®) for AMD has been reported in several regions including Europe, United States (US), Asia/Pacific, Africa/Middle East, and Central & South America.

The European Economic Area states of Bulgaria (Bulgarian Society of Ophthalmology), Finland (Finnish Medical Society, France (French Agency for the Safety of Health Products) Germany (German Ophthalmological Society), Ireland (Irish Governmental authorities), Norway (Norwegian Ophthalmological Society), Poland (Polish Ophthalmological Society), Sweden (Swedish Ophthalmological Society and Dental and Pharmaceutical Benefits Agency), as well as the United Kingdom (National Institute for Health and Care Excellence and Royal College of Ophthalmologists) have support for the off-label use of bevacizumab from the agency or society cited above (Bro et al 2020). The US FDA also supports the off-label use of Avastin® for AMD (FDA 2015).

A recent systematic review for managing nAMD reported the clinical experience with bevacizumab administered intravitreally includes 18,520 eyes and 77 populations (Veritti et al. 2022).

## SV.1 Post-authorisation exposure

Not applicable.

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

**Potential for misuse for illegal purposes**

Drugs that have a potential for misuse for illegal purposes are expected to share general characteristics such as psychoactive, stimulant, or sedative effects, or less commonly, anabolic effects or enhancement of haemoglobin levels. As there is no evidence that bevacizumab gamma is associated with psychostimulatory effects or dependency, a potential for it to be misused for illegal purposes is minimal.

Moreover, Lytenava is a medicinal product subject to restricted medical prescription, which is a limiting factor for illegal purposes usage.

# Part II: Module SVII - Identified and potential risks

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

| | |
|---|---|
| Important identified risks | • Endophthalmitis<br>• Intraocular inflammation<br>• Intraocular pressure increase<br>• Retinal detachment/tear |
| Important potential risks | • Thromboembolic events |
| Missing information | None |

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

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

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

Traumatic cataract has been reported to occur following intravitreal injections. It however has not been included as safety concerns in this RMP as it is considered risk with low frequency (see below) and considered acceptable in relation to the severity of nAMD. The event will be followed up via routine pharmacovigilance activities including signal detection and adverse reaction reporting.

Traumatic cataract

Intravitreal administration has been associated with traumatic cataracts caused by needle-induced damage from the injection procedure. However, cases of traumatic cataracts following intravitreal injections are rare, occurring in <0.1% injections (Petri 2020). In the Phase 3 studies, no cases of traumatic cataract following intravitreal injection with bevacizumab gamma were reported.

*Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):*

Retinal pigment epithelial tear has been reported to occur following intravitreal injections. This known risk is not included as safety concern in this RMP as it will be adequately addressed in the SmPC and Patient Information Leaflet and will be monitored via routine pharmacovigilance activities, including signal detection and adverse reaction reporting.

Retinal pigment epithelial tear

Retinal pigment epithelium (RPE) tears may occur spontaneously or after therapeutic intervention in patients with AMD. While RPE tears are a relatively frequent occurrence in patients with nAMD and are associated with pigment epithelial detachment (PED), they can also develop during anti-

VEGF therapy via intravitreal injection (Mitchell 2021). The pathogenesis of RPE tears following intravitreal anti-VEGF injections is not fully elucidated. It has been suggested that since anti-VEGF treatment can augment contraction of the choroidal neovascular membrane, the likelihood for developing an RPE tear is increased (Mitchell 2021). Following anti-VEGF intravitreal injections, the incidence of RPE tear has been reported to be 0.4% (Empeslidis 2014). A low incidence of RPE tear after treatment with bevacizumab gamma was observed in the Phase 3 studies, with only one case reported.

Other risks included in this category are the following:

Long term safety (beyond one year of treatment)

Long term safety of intravitreal bevacizumab is supported by the Guidance ICH E1 The Extent of Population Exposure to Assess Clinical Safety For Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions adopted by the European Commission on 1 November 1994 (CPMP/ICH/375/95), and the EMA Guidance Clinical Requirements for Locally Applied, Locally Acting Products, Containing Known Constituents (CPMP/EWP/239/95 final, dated JUNE 1996).

Since initial market approval in the United States on 26 February 2004, systemic bevacizumab has been approved for use in over 100 countries worldwide for various cancers (Bakri et al 2019) Chakravarthy et al 2012). Thus, the systemic side effects and safety of this product have been studied and monitored for nearly twenty years. Intravitreal injection of systemic anti-VEGF agents is generally thought to be characterised by lower systemic exposure and therefore a superior systemic safety, since the drug is confined in the intraocular environment and the intravitreal dose is much smaller than that used for intravenous treatment (Costagliola 2012).

When administered intravitreally, only a small fraction of bevacizumab enters systemic circulation (Moja 2014).

Studies have shown that there is no difference between bevacizumab and ranibizumab in terms of the risk of specific systemic adverse events (Bakri et al 2019; Martin 2011).

Based on the lack of new safety signals observed in the 1- and 2-year results of large randomised trials of either bevacizumab gamma, as Avastin used off-label, or ranibizumab (Chakravarthy 2013, Martin 2011), it is not expected that new safety signals will be identified following long-term treatment with bevacizumab gamma or that the safety profile following long-term treatment will be significantly different to the current safety profile. As such, long-term safety is not anticipated to impact the benefit-risk profile of bevacizumab gamma.

Treatment is administered by a physician with follow-up at regular intervals; thus, physicians can closely monitor the patient and the drug safety profile. Treatment can be withheld or discontinued if the patient risk profile or the drug safety profile changes over time as detailed in the product information (SmPC and Patient Information Leaflet).

Long-term safety studies are currently not planned and long-term safety will be monitored post-authorisation via signal detection and adverse reaction reporting.

Use during pregnancy

The nAMD (product indication) is most prevalent in patients over 65 years of age (Colijn 2017). Considering the age range of the intended population to be treated, it is unlikely that a pregnancy will occur in women following treatment with bevacizumab gamma. However, based on the anti-VEGF mechanism of action for bevacizumab gamma, a risk to embryofoetal development cannot be excluded and bevacizumab gamma should only be used during pregnancy if the potential benefit

outweighs the potential risks and women of child-bearing potential are recommended to use effective contraception during treatment.

Precautionary guidance regarding pregnancy and the use of contraceptives in women of child-bearing potential is provided in the SmPC (section 4.6) and Patient Information Leaflet (Section 2).

If bevacizumab gamma is nevertheless used in a pregnant woman, the pregnancy will be monitored closely with standard pharmacovigilance measures and will be summarised in Periodic Safety Update Reports (PSURs)/Periodic Benefit-Risk Evaluation Report (PBRERs).

*Known risks that do not impact the risk-benefit profile*

Immunogenicity

As a therapeutic protein, there is a potential for immunogenicity following bevacizumab gamma intravitreal injections. An elicited immunogenic response to a therapeutic protein can result in the production of anti-drug antibodies, which can lead to immune-mediated adverse events, decreased efficacy or altered pharmacokinetics. Intraocular inflammation has been associated with positive anti-drug antibodies following intravitreal injections of anti-VEGF treatments (Sharma 2020). However, while immunogenicity to anti-VEGF treatments have been reported in the literature, a clear link between safety signals and immune responses have yet been established (Wakshull 2017).

In the Phase 3 studies, no anti-drug antibodies were detected in subjects treated with bevacizumab gamma and only one case of intraocular inflammation following intravitreal injection was reported. Based on the overall database, immunogenicity is not expected to impact the benefit-risk profile of bevacizumab gamma and is consequently not included as a risk in this RMP. Immunogenicity is addressed in the SmPC and Patient Information Leaflet and will be monitored via routine PV activities.

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

**Important identified risk 1: Endophthalmitis**

Post-injection endophthalmitis is a rare risk following intravitreal injections.

Across the Phase 3 studies with bevacizumab gamma, only one treatment-emergent event of endophthalmitis (CTCAE Grade 3) was reported, which was considered to be related to treatment.

If proper aseptic conditions are adhered to during the intravitreal procedure, the impact of endophthalmitis on the benefit-risk profile of bevacizumab gamma is considered to be minimal.

**Important identified risk 2: Intraocular inflammation**

Intravitreal injections have been associated with intraocular inflammation, which is characterised by non-infectious inflammation that resolves without antibiotic treatment.

It 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.

Treatment is typically non-invasive, consisting of observation alone or topical corticosteroids (Cox 2021). Intraocular inflammation following intravitreal injections of anti-VEGF therapies are suggested to be due to either impurities stemming from the manufacturing, storage, preparation or handling of the anti-VEGF agents or to an inflammatory reaction to the treatments (Anderson 2021).

Intraocular inflammation following intravitreal injection is reported to occur in 0.02-0.16% cases (Daien 2018, Williams 2016). In the Phase 3 studies, there was an overall low incidence of intraocular inflammation following treatment with bevacizumab gamma, with only one case reported.

Proper aseptic injection techniques must always be used when administering bevacizumab to reduce the impact on the benefit-risk profile of the product. At this purpose the product information includes a warning (SmPC sections 4.3, 4.4 and 4.8 and PL section 2 and 4) to prevent intraocular inflammation. Furthermore the patient guide will provide guidance for the patient when to see a doctor.

**Important identified risk 3: Intraocular pressure increase**

Intraocular injections could lead to a transient increase in intraocular pressure (IOP) due to the rapid increase in fluid volume in the vitreous cavity (Kiddee 2015, Schargus 2020). The injected volume of bevacizumab may influence the IOP increase. These increases generally resolving within a few hours post-injection.

In the Phase 3 studies with bevacizumab gamma, intraocular pressure increases were common, occurring in 8 (2.3%) subjects. The majority of cases were mild in severity and resolved without sequelae. Two (0.6%) cases were reported as serious adverse events, both which were considered not related to the study drug but rather to the intravitreal procedure.

IOP is a known risk and well characterised in the clinical practice as well. The product information includes a warning (SmPC Section 4.4, 4.8 and 4.9 and Patient Information Leaflet Section 2) to prevent it. Furthermore the patient guide will provide guidance for the patient when to see a doctor.

**Important identified risk 4: Retinal detachment/tear**

Intravitreal injections have been associated with rhegmatogenous retinal detachment and retinal tears. Rhegmatogenous retinal detachments are caused by fluid passing from the vitreous cavity through a retinal tear or break into the potential space between the sensory retina and the retinal pigment epithelium (Blair 2022).

Retinal detachment leads to visual distortion, and untreated retinal detachment leads to retinal cell death and loss of vision.

Rhegmatogenous retinal detachment are reported to occur at a rate of 0.013-0.03% intravitreal injections (Gabrielle 2022, Storey 2019). No incidence of retinal detachment or retinal tear was reported in the study eye following treatment with bevacizumab gamma in the Phase 3 studies.

Retinal detachment / tear is a known risk and well characterised in the clinical practice as well. The product information includes a warning (SmPC sections 4.4, 4.8 and PL sections 2 and 4) to prevent it. Furthermore the patient guide will provide guidenace for the patient when to see a doctor.

**Important potential risk 1: Thromboembolic events**

In the Phase 3 studies, there was a low rate of thromboembolic events (ATEs) observed in nAMD patients treated with bevacizumab gamma. The incidence of reported ATEs was 1.5% (5/341) in patients treated with bevacizumab gamma compared to 2.8% (4/145) in patients treated with ranibizumab. One patient treated with ONJ-5010 experienced an event of pulmonary embolism. The TEs were generally not considered related to bevacizumab gamma and were reported in patients with cardiovascular risk factors, which may have contributed to the development of TEs. The impact of TEs on the benefit-risk profile of bevacizumab gamma is therefore considered to be low.

## 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 1: Endophthalmitis**

Potential mechanisms:

Intravitreal injections of anti-VEGF and other intravitreally applied drugs have been associated with cases of endophthalmitis. Contaminated surgical equipment/area, breaches in the sterile field and use of poor aseptic techniques for intravitreal injections are thought to be the primary mechanisms which introduce infection-causing microorganisms to the eye.

Evidence source(s) and strength of evidence:

The important identified risk of endophthalmitis has been extensively documented in literature on approved anti-VEGF intravitreal injections and is further based on data from the Phase 3 studies (ONS-5010-001, ONS-5010-002 and ONS-5010-003).

Characterisation of the risk:

While the rate of infectious endophthalmitis following intravitreal injection is low, with a reported incidence between 0.019% and 0.1% per injection (Kiss 2018, Lau 2018), it is one of the most concerning complications associated with anti-VEGF therapy. Outbreaks of bacterial endophthalmitis following anti-VEGF injections may result in vision loss from vitreous opacity, retinal detachment, and in particularly severe cases, globe loss due to infectious, inflammatory, and fibrotic processes. Endophthalmitis is an ophthalmic emergency and requires appropriate and prompt therapy (Barnes et al 2021).

In the Comparison of AMD Treatment Trials (CATT), 11 eyes developed endophthalmitis after 18,509 injections in 1185 patients, with an incidence rate per injection of 0.06% (95% Confidence Interval [0.03%, 0.11%]) or 1 per 1,700 injections (Martin 2011, Meredith 2015). Similarly, in the MARINA study, a rate of 0.05% per injection of ranibizumab was reported (Rosenfeld 2006).

These results align with an extensive meta-analysis involving 350,535 intravitreal anti-VEGF treatment, which reported a rate of 0.056% per injection (Fileta 2014).

A further meta-analysis reported on specific anti-VEGF treatments with 818,558 injections in 156,594 patients with nAMD. Here, the calculated the rates of endophthalmitis following aflibercept, bevacizumab (as Avastin), and ranibizumab intravitreal injections were 0.100% (136/135,973), 0.056% (268/481,572), and 0.047% (94/201,013), respectively (Kiss 2018).

A study, Bavinger et al 2004, evaluated 1,095,305 intravitreal injections and found that when grouped together, ranibizumab and aflibercept, had higher odds of post-injection endophthalmitis than bevacizumab (OR=1.29, p=0.02). Individually, aflibercept was marginally associated with a higher odds of post-injection endophthalmitis compared to bevacizumab (OR:1.34, p=0.06). Ranibizumab may have a higher odds ratio for endophthalmitis compared to bevacizumab (OR:1.25), but the statistical support for this possibility was not strong (p=0.08).

Studies of previously reported outbreaks of bevacizumab-associated endophthalmitis concluded that the most likely cause was contamination during the compounding process. Lyteneva is a restricted medical

prescription-only medication available in single use glass vials unlike off-label bevacizumab injections which is compounded in pharmacies or clinics. A study, Mccannel et al 2014, concluded that coagulase-negative Staphylococcus was the most common bacterial culture isolate followed by Streptococcal isolates. Streptococcal isolates (oral commensals) were more frequent after intravitreal anti-vascular endothelial growth factor injection than after intraocular surgery. Therefore, strategies to minimise oropharyngeal droplet transmission including avoidance of talking, coughing, and sneezing or wearing surgical masks should be considered during these injections. Endophthalmitis cannot be prevented entirely, but its incidence can be reduced by ensuring adequate sterile precautions and the use of prophylactic antibiotics.

Across the Phase 3 studies with bevacizumab gamma, only one treatment-emergent event of endophthalmitis (CTCAE Grade 3) was reported and was considered related to treatment.

Risk factors:

Performing the intravitreal procedure under improper aseptic conditions increases the risk of endophthalmitis. Furthermore, patients with active ocular infection or intraocular inflammation have an increased risk of developing endophthalmitis.

Preventability:

The risk of endophthalmitis can be reduced by performing the intravitreal procedure under aseptic conditions, including use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum. Patients with active ocular infection or inflammation should not be treated with bevacizumab gamma.

Patients should be monitored for any signs or symptoms of endophthalmitis following intravitreal injection and they should be instructed to recognize and report symptoms typically related to endophthalmitis.

Impact on the risk-benefit balance of the product:

Symptoms of endophthalmitis following intravitreal injections generally develop between one and six days after the inciting injection (mean: 2.5 days), and presentation occurs at day three or four on average (range: one to 15 days) (Sachdeva 2016).

Decreased vision is present in virtually every patient (94–100%), as is pain (94–100%) (Sachdeva 2016). Visual acuity at presentation can vary from 20/80 to hand motion, but is worse than 20/100 in more than 80% of patients (Sachdeva 2016). In severe cases and if not treated promptly, endophthalmitis can lead to a complete loss of vision in the affected eye.

If adequately and timely treated, endophthalmitis usually resolves without sequelae. Following sampling via intravitreal tap, endophthalmitis is generally treated with injectable antibiotics, usually vancomycin and ceftazidime, often in conjunction with intravitreal steroids. If a patient only has perception of light, a pars plana vitrectomy procedure can be performed(Niyadurupola 2018).

Based on the low reporting rate of endophthalmitis following intravitreal injection in the literature, the data available to date from the clinical development programme for bevacizumab gamma, and reported events being generally manageable with treatment, the impact of endophthalmitis on the benefit-risk profile of bevacizumab gamma is considered low.

Public health impact

The risk is uncommon (≥1/1,000 to <1/100). Furthermore, it has been adequately addressed and included in Sections 4.2 and 4.4 of the SmPC and Sections 2 and 4 of the PL and the patient/carer guide. Overall, no public health impact is expected if the proper aseptic conditions are followed.

**Important Identified Risk 2: Intraocular inflammation**

Potential mechanism:

Intravitreal injections of anti-VEGF therapies, including those with bevacizumab, have been associated with intraocular inflammation.

Intraocular inflammation are suggested to be due to either impurities stemming from the manufacturing, storage, preparation or handling of the anti-VEGF agents or to an inflammatory reaction to the treatments (Anderson 2021).

Evidence source(s) and strength of evidence:

According to retrospective case and database analysis, conducted to evaluate outcomes of infectious and non-infectious endophthalmitis after intravitreal injections (IVTs) of anti-VEGF agents from 2006 to 2013, intraocular inflammation following intravitreal injection is reported to occur in 0.02-0.16% cases (Daien 2018, Williams 2016).

In the Phase 3 studies, there was an overall low incidence of intraocular inflammation following treatment with bevacizumab gamma, with only one case reported. Iritis was reported in the study eye of one study subject following the 4th monthly dose of bevacizumab gamma. The iritis was considered severe, but not serious. The eye was treated with fluorometholone for 45 days and resolved. The study drug dosing was not altered and the study subject completed the full 12 months of study participation.

Characterisation of the risk:

Intraocular inflammation is a non-infective acute inflammatory response that can cause eye pain, worsening eye redness, blurred vision, increase sensitivity to light and in sometimes even lead to vision decrease.

Risk factors:

There are no large study data for bevacizumab which identified risk factors for the event. However, bevazicumab is a therapeutic protein which may cause immunogenicity and a local inflammatory response. Patients with an acute inflammation of the eye may be at an increased risk. In a small series of patients treated with brolucizumab risk factors for intraocular inflammation were old age, female sex, and history of diabetes (Mukai R 2021).

Preventability:

Proper aseptic injection techniques must always be used when administering bevacizumab. In addition, patients should be monitored during the week following the injection to grant early treatment if an inflammation occurs. Adult patients should be instructed to report any symptoms suggestive of an intraocular inflammation without delay.

Impact on the risk-benefit balance of the product:

Based on the data available from literature and clinical development programme for bevacizumab gamma and considering that intraocular inflammation has been proven to be non-infectious and resolving spontaneously without antibiotic administration or applying local corticosteroids (Cox 2021), the impact on the benefit-risk balance for bevacizumab is considered low.

Public health impact:

The reporting rate of intraocular inflammation following an intravitreal injection of bevacizumab for approved indications is low. Furthermore, it has been adequately addressed and included in the product information (SmPC sections 4.3, 4.4 and 4.8 and PL section 2 and 4).

Overall, no public health impact is expected if the proper aseptic conditions are followed.

**Important Identified Risk 3: Intraocular pressure increase**

Potential mechanism:

Intravitreal injection of bevacizumab can lead a transient increase in IOP due to the rapid increase in fluid volume in the vitreous cavity (Kiddee 2015, Schargus 2020).

IOP and perfusion of the optic nerve head should be monitored and managed appropriately.

Evidence source(s) and strength of evidence:

Published data and Phase 3 clinical trials. In all clinical studies of bevacizumab gamma, IOP was measured in both eyes by applanation tonometry at all study visits prior to injection of bevacizumab gamma as well as 30 minutes following the injection.

Characterisation of the risk:

In the Phase 3 studies with bevacizumab gamma, intraocular pressure increases were common, occurring in 8 (2.3%) subjects. The majority of cases were mild in severity and resolved without sequelae. Two (0.6%) cases were reported as serious adverse events, both which were considered not related to the study drug but rather to the intravitreal procedure.

Risk factors:

Pre-existing high IOP; bevacizumab should not be administered in the event of an intraocular pressure ≥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 intravitreal injection of bevacizumab has been consistent over the years and this risk is well-characterised. As elevations in intraocular pressure following intravitreal injection are generally transient and self-resolving, we assume that the benefit risk balance remains positive for bevacizumab.

Public health impact:

The reporting rate of IOP increase following an intravitreal injection of bevacizumab for approved indications is low.

Furthermore, IOP increase is a known risk and is well characterised in clinical practice. It is adequately addressed within the SmPC (Sections 4.4, 4.8 and 4.9) and Patient Information Leaflet (Section 2).

**Important Identified Risk 4: Retinal detachment/tear**

Potential mechanism:

Intravitreal injections have been associated with rhegmatogenous retinal detachment and retinal tears. 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. Complete ocular exams were performed at each study visit, prior to injection to detect any adverse events. Exams included IOP, slit lamp, dilated ophthalmoscopy, and imaging (spectral domain optical coherence tomography).

Characterisation of the risk:

Rhegmatogenous retinal detachment are reported to occur at a rate of 0.013-0.03% intravitreal injections (Gabrielle 2022, Storey 2019). No incidence of retinal detachment or retinal tear was reported in the study eye following treatment with bevacizumab gamma in the Phase 3 studies.

Risk factors:

Conditions might increase the risk for retinal detachment are the following: previous retinal detachment or retinal tear, eye tumors, inflammation in the choroid or the retina, eye injury, high myopia or severe high blood pressure.

Preventability:

In most cases a retinal detachment or retinal tear cannot be prevented.

Proper aseptic injection techniques should always be used when administering the medicinal product.

Treatment should be discontinued in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes.

Impact on the risk-benefit balance of the product:

It is considered a known risk associated to intravitreal injection and well characterised in the clinical practice, therefore it is assumed that the benefit-risk balance remains positive for bevacizumab.

Public health impact:

The reporting rate of retinal detachment and retinal tear following an intravitreal injection of bevacizumab is considered low. Furthermore, retinal detachment / tear is a known risk and the product information includes a warning (SmPC sections 4.4, 4.8 and PL sections 2 and 4) to prevent it.

**Important Potential Risk 1: Thromboembolic events**

Potential mechanisms:

There is a potential risk of thromboembolic events (TEs), including arterial thromboembolic events defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause) as well as venous thrombotic events (VTE) defined as deep vein thrombosis and pulmonary embolism associated with VEGF inhibition. Inhibition of the VEGF pathway may impair angiogenesis, increase vascular inflammation, disrupt vascular integrity, and disturb the normal EC interaction with platelets, which may compromise the integrity of the EC lining and promote platelet aggregation, thereby increasing the risk of TE events.

Evidence source(s) and strength of evidence:

The important potential risk of thromboembolic events has been extensively documented in literature on approved anti-VEGF intravitreal injections and is further based on data from the Phase 3 studies (ONS-5010-001, ONS-5010-002 and ONS-5010-003).

Characterisation of the risk:

TEs are one of the more common complications of systemic anti-VEGF agents. Intravitreal injection of these agents is generally thought to be characterised by lower systemic exposure and therefore a superior systemic safety, since the drug is confined in the intraocular environment and the intravitreal dose is much smaller than that used for intravenous treatment (Costagliola 2012). Although there is an increased risk of TEs after intravenously administered high doses of VEGF-inhibitors for the treatment of cancer, there is currently no evidence of increased incidences of TEs for the much lower intravitreally administered doses of VEGF-inhibitors in patients with nAMD.

Incidence varies across published studies and has been reported to range between 0.68% and 6.0% for ATE (Boyer 2009, Busbee 2013, Chakravarthy 2012, Martin 2011, Zarbin 2017).

In the Phase 3 studies, there was a low rate of TEs observed in nAMD patients treated with ONS-5010. The incidence of reported ATEs in the bevacizumab gamma studies was 1.5% (5/341) in patients treated with bevacizumab gamma compared to 2.8% (4/145) in patients treated with ranibizumab. The rate of VTE was very low with one bevacizumab treated patient experiencing pulmonary embolism.

In the CATT trial, arteriothrombotic events were reported in 5.0% (29/586) bevacizumab-treated patients and venous thrombotic events occurred in 1.7% (10/586) bevacizumab-treated patients after 2 years (Martin 2012).

In the Lucentis Compared to Avastin Study (LUCAS), arteriothrombotic events were reported in 4.1% (9/220) bevacizumab-treated patients and no venous thrombotic events were reported in bevacizumab-treated patients after 2 years (Berg 2015).

Risk factors:

Patients with cardiovascular risk factors, a medical history of TE or clotting disorders potentially have a higher risk for ATEs, VTEs, non-ocular haemorrhage and hypertension.

Preventability:

Patients with CV comorbidities or a previous history of coagulation disorders, VTE, myocardial infarction and cerebral vascular accidents may potentially be at an increased risk of TE events. Patients with known risk factors should be informed of this risk via educational materials, and monitored following treatment with bevacizumab gamma.

Treatment with intravitreal bevacizumab is administered by a physician with follow-up at regular intervals. Thus, a patient/carer guide and patient information leaflet can be provided during the initial patient visit before treatment is initiated; and the physician can closely monitor the patient and the drug safety profile at each treatment interval. Also, the drug administration and monitoring schedule

can be individualised for patients with CV comorbidities or other risk factors such as a previous history of DVT, myocardial infarction and cerebral vascular accidents.

Impact on the risk-benefit balance of the product:

While TEs have been reported following anti-VEGF intravitreal injections in the literature, there were few events observed following treatment with bevacizumab gamma. The events that were seen in the Phase 3 studies were generally not considered related to bevacizumab gamma and were reported in patients with cardiovascular risk factors, which may have contributed to the development of TEs. The impact of TEs on the benefit-risk profile of bevacizumab gamma is therefore considered to be low.

Public health impact:

Although there were few reported cases in the Phase 3 studies, there is a theoretical risk of TEs in patients treated with bevacizumab gamma. Considering this theoretical risk, the frequency of TEs following bevacizumab gamma is expected to be common (≥1/100 to <1/10) in patients with cardiovascular risk factors. The risk has been included in Section 4.4 of the SmPC, Section 2 of the PL, and the patient/carer guide.

**SVII.3.2. Presentation of the missing information**

Not applicable.

# Part II: Module SVIII – Summary of the safety concerns

**Table 11: Summary of safety concerns**

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | • Endophthalmitis<br>• Intraocular inflammation<br>• Intraocular pressure increase<br>• Retinal detachment/tear |
| Important potential risks | • Thromboembolic events |
| Missing information | • None |

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

## III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting, regular monitoring global literature for screening of safety information, risk-benefit analysis through periodic aggregate data analysis like PSURs / PBRERs, and signal detection:

**Specific adverse reaction follow-up questionnaires**

Specific follow-up modules will be used to collect specific data useful for the characterization and/or closely monitoring of the respective safety concerns listed below:

- Endophthalmitis
- Thromboembolic events in the eye(s)

The guided questionnaires are provided in Annex 4. The pharmacovigilance department will reach out to the reporter with a request to complete the questionnaire when a suspected or diagnosed case for endophthalmitis or thromboembolic events in the eyes(s) occurring after intravitreal injection of bevacizumab is identified.

**Other forms of routine pharmacovigilance activities:**

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

### III.2 Additional pharmacovigilance activities

None.

### III.3 Summary Table of additional Pharmacovigilance activities

Not applicable. No additional pharmacovigilance activities are proposed.

## Part IV: Plans for post-authorisation efficacy studies

Not applicable. There are no planned or ongoing imposed post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

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

## Risk Minimisation Plan

## V.1. Routine Risk Minimisation Measures

**Table 12: Description of routine risk minimisation measures by safety concern**

| Safety concern | Routine risk minimisation activities |
|---|---|
| **Important identified risks** | |
| Endophthalmitis | Routine risk communication:<br><br>SmPC<br><br>Section 4.2 Posology and method of administration<br><br>Section 4.3 Contraindication<br><br>Section 4.4 Special warnings and precautions for use<br><br>Section 4.8 Undesirable effects<br><br>Patient Information Leaflet (PL)<br><br>Section 2 What you need to know before you use Lytenava<br><br>Section 4 Possible side effects<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br><br>Recommendation for performing intravitreal injection procedure under aseptic conditions presented in SmPC Section 4.2, 6.6 and PL Section 3 as well as in the Information intended for HCP only – Method of administration.<br><br>Recommendation for instructing patients to report any symptoms without delay in SmPC Section 4.4. Instructions on how to detect early signs and symptoms of endophthalmitis are provided in PL Sections 2 and 4.<br><br>Other routine risk minimisation measures beyond the Product Information:<br><br>Pack size: one vial for single use only.<br><br>Legal Status<br><br>Lytenava is only available by prescription. It must be administered by a qualified ophthalmologist experienced in intravitreal injections and under aseptic conditions. |

| | |
|---|---|
| Intraocular inflammation | Routine risk communication :<br>SmPC<br>Section 4.3 Contraindication<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects<br>Patient Information Leaflet (PL)<br>Section 2 What you need to know before you use Lytenava<br>Section 4 Possible side effects<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>Recommendation for performing intravitreal injection procedure under aseptic conditions presented in SmPC Section 4.2, 6.6 and PL Section 3 as well as in the Information intended for HCP only – Method of administration.<br>Recommendation for instructing patients to report any symptoms without delay in SmPC Section 4.4 Instructions on how to detect early signs and symptoms of intraocular inflammation are provided in PL Sections 2 and 4.<br>Other routine risk minimisation measures beyond the Product Information:<br>Pack size: one vial for single use only.<br>Legal Status:<br>Lytenava is only available by prescription. It must be administered by a qualified ophthalmologist experienced in intravitreal injections and under aseptic conditions. |
| Intraocular pressure increase | Routine risk communication:<br>SmPC<br>Sections 4.4 Special warnings and precautions for use<br>Section 4.8 Undesiderable effects<br>Section 4.9 Overdose<br>Patient Information Leaflet (PL)<br>Section 2 What you need to know before you use Lytenava<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>Recommendation for performing intravitreal injection procedure under aseptic conditions presented in SmPC Section 4.2, 6.6 and |

| | |
|---|---|
| | PL Section 3 as well as in the Information intended for HCP only – Method of administration.<br><br>Recommendation for instructing patients to report any symptoms without delay in SmPC Section 4.4 Instructions on how to detect early signs and symptoms of intraocular pressure increase are provided in PL Sections 2 and 4.<br><br>Other routine risk minimisation measures beyond the Product Information:<br><br>Pack size: one vial for single use only.<br><br>Legal Status:<br><br>Lytenava is only available by prescription. It must be administered by a qualified ophthalmologist experienced in intravitreal injections and under aseptic conditions. |
| Retinal detachment/tear | Routine risk communication:<br><br>SmPC<br><br>Sections 4.4 Special warnings and precautions for use<br><br>Section 4.8 Undesiderable effects<br><br>Patient Information Leaflet (PL)<br><br>Section 2 What you need to know before you use Lytenava<br><br>Section 4 Possible side effects<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br><br>Recommendation for performing intravitreal injection procedure under aseptic conditions presented in SmPC Section 4.2, 6.6 and PL Section 3 as well as in the Information intended for HCP only – Method of administration.<br><br>Recommendation for instructing patients to report any symptoms without delay in SmPC Section 4.4 Instructions on how to detect early signs and symptoms of retinal detachment/tear are provided in PL Sections 2 and 4.<br><br>Other routine risk minimisation measures beyond the Product Information:<br><br>Pack size: one vial for single use only.<br><br>Legal Status:<br><br>Lytenava is only available by prescription. It must be administered by a qualified ophthalmologist experienced in intravitreal injections and under aseptic conditions. |
| **Important potential risk** | |

| | |
|---|---|
| Thromboembolic events | Routine risk communication:<br>SmPC<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects<br>Patient Information Leaflet<br>Section 2 What you need to know before you use Lytenava<br>Section 4 Possible side effects<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>Not applicable.<br>Other routine risk minimisation measures beyond the Product Information:<br>Pack size: one vial for single use only.<br>Legal Status<br>Lytenava is only available by prescription.It must be administered by a qualified ophthalmologist experienced in intravitreal injections and under aseptic conditions. |
| | |
| **Missing information** | |
| None | None |

## V.2. Additional Risk Minimisation Measures

**Additional risk minimisation: Patient information pack (Patient/care-giver guide and patient information leaflet)**

Objectives:

The objective of the patient information pack is to provide:

- A description of neovascular age-related macular degeneration (nAMD)
- A description of Lytenava, how it works, and what to expect from treatment with Lytenava
- A description of the key signs and symptoms of the key risks associated with Lytenava, like local eye effects (i.e., infectious endophthalmitis, intraocular pressure increase, intraocular inflammation, retinal detachment and retinal tear) and thromboembolic events after intravitreal injection of bevacizumab
- A description of when to seek urgent attention from the health care provider should signs and symptoms of these risks present themselves
- Recommendations for adequate care after the injection
- Provide detailed information on correct use of the product and warning to avoid the off label use in special population, including but not limited to children and adolescent under 18 years

The patient information pack is also available as audiovisual educational material online and can be viewed by scanning a QR code on the Patient Guide provided to the physician for distribution to the patient after bevacizumab is prescribed to them.

Rationale for the additional risk minimisation activity:

Treatment is administered by a physician with follow-up at regular intervals; thus, physicians can closely monitor the patient and the drug safety profile. The drug administration and monitoring schedule can be individualised for patients with CV comorbidities or a previous history of myocardial infarction and cerebral vascular accidents. Treatment can be withheld or discontinued if the patient risk profile changes over time.

The patient/ carer guide provides instructions to patients for early recognition of key signs and symptoms of potential adverse reactions, and timely reporting to their physicians, encouraging prompt intervention to reduce the risk of serious complications. It aims to promote awareness and understanding of the information contained within the Patient Information Leaflet and inform patients/carers of the risks, the key signs and symptoms of those risks, and when to seek urgent attention from their physician in order to minimise the incidence of the risks and promote communication between the patient and their physician.

Key signs and symptoms of the following important identified and important potential risks are covered in the patient information booklet:

***Endophthalmitis (risk 1 - important identified)***

- 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 (risk 2 - important identified)***

- Intraocular inflammation can cause eye pain, worsening eye redness, blurred vision and/or increased sensitivity to light.

***Intraocular pressure increase (risk 3 - important identified)***

- Increases in intraocular pressure (IOP) within 60 minutes of injection of bevacizumab are very common. They may be asymptomatic, or could cause eye pain and decreased vision.

***Retinal detachment/tear (risk 4 - important identified)***

- Warning signs may include symptoms such as increased eye discomfort, light flashes and blurred or decreased vision.

***Thromboembolic events (risk 1 - important potential)***

- Warning signs for myocardial infarction may include acute chest pain radiating to the back, jaw or left arm, anxiety, greyish skin tone or acute onset shortness of breath and weakness
- Warning signs of cerebrovascular accident / stroke may include slurred or disturbed speech, numbness or paralysis of limbs, dizziness or strong headache

- Warning signs of venous thrombotic events may include pain, skin color changes and swelling of a limb

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 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 bevacizumab in a new indication (according to the national legislation in the respective countries), and the distribution of the material to all ophthalmology clinics where bevacizumab is expected to be used in adult patients. It should be provided during a patient's initial visit to the physician's office.

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

Success of the proposed risk minimisation measures will be evaluated by monitoring of incidence and severity of spontaneous reporting rate of the adverse events included in the list of safety concerns and will be discussed periodically in the PSURs / PBRERs.

## V.3 Summary of risk minimisation measures

**Table 13: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern**

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Endophthalmitis | Routine risk minimisation measures | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>Questionnaire for follow-up of post-marketing case report (Annex 4)<br><br>Additional pharmacovigilance activities:<br>None |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | SmPC<br>Section 4.2 Posology and method of administration<br>Section 4.3 Contraindications<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesiderable effects<br>Section 6.6 Special precautions for disposal and other handling<br>Patient Information Leaflet (PL)<br>Section 2 What you need to know before you use Lytenava<br>Section 4 Possible side effects<br>Recommendation regarding proper aseptic conditions to follow when administering Lytenava<br>Legal status: Lytenava is by prescription only<br>Additional risk minimisation measures:<br>Patient information pack (Patient/care-giver guide and patient information leaflet) | |
| Intraocular inflammation | Routine risk minimisation measures | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>None |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | SmPC<br>Section 4.3 Contraindication<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects<br>Section 6.6 Special precautions for disposal and other handling<br><br>Patient Information Leaflet (PL)<br>Section 2 What you need to know before you use Lytenava<br>Section 4 Possible side effects<br>Recommendation regarding proper aseptic conditions to follow when administering Lytenava<br>Legal status: Lytenava is by prescription only<br>Additional risk minimisation measures: Patient information pack (Patient/care-giver guide and patient information leaflet) | |
| Intraocular pressure increase | Routine risk minimisation measures | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>None |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | SmPC<br>Sections 4.4 Special warnings and precautions for use<br>Section 4.8 Undesiderable effects<br>Section 4.9 Overdose<br>Section 6.6 Special precautions for disposal and other handling<br><br>Patient Information Leaflet (PL)<br>Section 2 What you need to know before you use Lytenava<br>Section 4 Possible side effects<br>Recommendation regarding proper aseptic conditions to follow when administering Lytenava<br>Legal status: Lytenava is by prescription only<br>Additional risk minimisation measures: Patient information pack (Patient/care-giver guide and patient information leaflet) | |
| Retinal detachment/tear | Routine risk minimisation measures | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>None |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | SmPC<br>Sections 4.4 Special warnings and precautions for use<br>Section 4.8 Undesiderable effects<br>Section 6.6 Special precautions for disposal and other handling<br><br>Patient Information Leaflet (PL)<br>Section 2 What you need to know before you use Lytenava<br>Section 4 Possible side effects<br>Recommendation regarding proper aseptic conditions to follow when administering Lytenava<br>Legal status: Lytenava is by prescription only<br>Additional risk minimisation measures: Patient information pack (Patient/care-giver guide and patient information leaflet) | |
| Thromboembolic events | Routine risk minimisation measures<br>SmPC<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects<br>Patient Information Leaflet (PL)<br>Section 2 What you need to know before you use Lytenava<br>Section 4 Possible side effects<br>Legal status: Lytenava is by prescription only<br>Additional risk minimisation | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:Questionnaire for follow-up of post-marketing case report (Annex 4)<br><br>Additional pharmacovigilance activities:<br>None |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | measures: Patient information pack (Patient/care-giver guide and patient information leaflet) | |

# Part VI: Summary of the risk management plan

# Summary of risk management plan for Lytenava (bevacizumab gamma)

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

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

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

## I. The medicine and what it is used for

Lytenava is authorised for treatment of neovascular (wet) age-related macular degeneration (AMD) (see SmPC for the full indication). It contains bevacizumab gamma as the active substance and it is given by intravitreal injection

Further information about the evaluation of Lytenava's benefits can be found in Lytenava's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage ema.europa.eu/medicines/human/EPAR/lytenava.

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

Important risks of Lytenava, together with measures to minimise such risks and the proposed studies for learning more about Lytenava'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 patient information 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 Lytenava, 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, 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 Lytenava 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 Lytenava. 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;

| **List of important risks and missing information** | |
|---|---|
| Important identified risks | Endophthalmitis<br>Intraocular inflammation<br>Intraocular pressure increase<br>Retinal detachment/tear |
| Important potential risks | Thromboembolic events |
| Missing information | None |

## *II.B Summary of important risks*

| **Important identified risk: Endophthalmitis** | |
|---|---|
| Evidence for linking the risk to the medicine | The important identified risk of endophthalmitis is based on data from the Phase 3 studies (ONS-5010-001, ONS-5010-002 and ONS-5010-003) and has been extensively documented in literature on approved anti-VEGF intravitreal injections. |
| Risk factors and risk groups | Performing the intravitreal procedure under improper aseptic conditions increases the risk of endophthalmitis. Furthermore, patients with active ocular infection or intraocular inflammation have an increased risk of developing endophthalmitis. |
| Risk minimisation measures | Routine risk minimisation measures: |

| | |
|---|---|
| | SmPC<br>Section 4.2 Posology and method of administration<br>Section 4.3 Contraindication<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects<br>Section 6.6 Special precautions for disposal and other handling<br>Patient Information Leaflet (PL)<br>Section 2 What you need to know before you use Lytenava<br>Section 4 Possible side effects<br>Recommendation regarding proper aseptic conditions to follow when administering Lytenava.<br>Legal status: Lytenava is by prescription only<br>Additional risk minimisation measures:<br>Patient information pack (Patient/care-giver guide and patient information leaflet) |
| Additional pharmacovigilance activities | None |
| **Important identified risk: Intraocular inflammation** | |
| Evidence for linking the risk to the medicine | Intravitreal injections of anti-VEGF therapies, including those with bevacizumab, have been associated with intraocular inflammation.<br>Intraocular inflammations are suggested to be due to either impurities stemming from the manufacturing, storage, preparation or handling of the anti-VEGF agents or to an inflammatory reaction to the treatments.<br>Intraocular inflammation can cause eye pain, worsening eye redness, blurred vision, increase sensitivity to light and in sometimes even lead to vision decrease. |
| Risk factors and risk groups | Proper aseptic injection techniques must always be used when administering bevacizumab. |
| Risk minimisation measures | Routine risk minimisation measures: |

| | |
|---|---|
| | SmPC<br>Section 4.3 Contraindication<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects<br>Section 6.6 Special precautions for disposal and other handling<br>Patient Information Leaflet (PL)<br>Section 2 What you need to know before you use Lytenava<br>Section 4 Possible side effects<br>Recommendation regarding proper aseptic conditions to follow when administering Lytenava.<br>Legal Status: Lytenava is by prescription only.<br>Additional risk minimisation measures:<br>Patient information pack (Patient/care-giver guide and patient information leaflet) |
| Additional pharmacovigilance activities | None. |
| **Important identified risk: Intraocular pressure increase** | |
| Evidence for linking the risk to the medicine | Intravitreal injection of bevacizumab can lead a transient increase in IOP due to the rapid increase in fluid volume in the vitreous cavity. |
| Risk factors and risk groups | Pre-existing high IOP. |
| Risk minimisation measures | Routine risk minimisation measures: |

| | |
|---|---|
| | SmPC<br>Sections 4.4 Special warnings and precautions for use<br>Section 4.8 Undesiderable effects<br>Section 4.9 Overdose<br>Section 6.6 Special precautions for disposal and other handling<br>Patient Information Leaflet (PL)<br>Section 2 What you need to know before you use Lytenava<br>Section 4 Possible side effects<br>Recommendation regarding proper aseptic conditions to follow when administering Lytenava.<br>Legal Status: Lytenava is by prescription only.<br>Additional risk minimisation measures:<br>Patient information pack (Patient/care-giver guide and patient information leaflet) |
| Additional pharmacovigilance activities | None. |
| **Important identified risk: Retinal detachment/tear** | |
| Evidence for linking the risk to the medicine | Intravitreal injections have been associated with rhegmatogenous retinal detachment and retinal tears. Rhegmatogenous retinal detachment occurs when the liquefied vitreous enters between the choroid and the pigmented epithelium detaching the retinal layer from the underlying choroid.<br>Traction retinal detachment occurs when scar tissue or other abnormal tissue grows on the surface of the retina, pulling the retina away from the layer beneath it. This does not necessarily cause a specific tear or break in the retina. In patients with advanced stages of ROP, retinal detachment develops when neovascularisation progresses and proliferous fibrous and vascular tissue lead to traction at the demarcation zone between vascular and avascular retina often thickened into an ophthalmoscopically visible ridge.<br>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.<br><br>Retinal detachment leads to visual distortion, and untreated retinal detachment leads to retinal cell death and loss of vision. |
| Risk factors and risk groups | Previous retinal detachment or retinal tear, eye tumours, inflammation in the choroid or the retina, eye injury, high myopia or severe high blood pressure. |
| Risk minimisation measures | Routine risk minimisation measures:<br><br>SmPC<br><br>Sections 4.4 Special warnings and precautions for use<br><br>Section 4.8 Undesiderable effects<br><br>Section 6.6 Special precautions for disposal and other handling<br><br>Patient Information Leaflet (PL)<br><br>Section 2 What you need to know before you use Lytenava<br><br>Section 4 Possible side effects<br><br>Recommendation fregarding proper aseptic conditions to follow when administering Lytenava.<br><br>Legal Status: Lytenava is by prescription only.<br><br>Additional risk minimisation measures:<br><br>Patient information pack (Patient/care-giver guide and patient information leaflet) |
| Additional pharmacovigilance activities | None. |
| **Important potential risk: Thromboembolic events** | |
| Evidence for linking the risk to the medicine | The important potential risk of thromboembolic events is based on data from the Phase 3 studies (ONS-5010-001, ONS-5010-002 and ONS-5010-003) and has been extensively documented in literature on approved anti-VEGF intravitreal injections. |
| Risk factors and risk groups | Patients with cardiovascular risk factors or clotting disorders have a higher risk for ATEs, VTEs, non-ocular haemorrhage and hypertension. |
| Risk minimisation measures | Routine risk minimisation measures: |

| | |
|---|---|
| | SmPC<br>Section 4.4 Special warnings and precautions for use<br>Section 4.8 Undesirable effects<br>Patient Information Leaflet (PL)<br>Section 2 What you need to know before you use Lytenava<br>Section 4 Possible side effects<br>Legal Status: Lytenava is by prescription only.<br>Additional risk minimisation measures:<br>Patient information pack (Patient/care-giver guide and patient information leaflet) |
| Additional pharmacovigilance activities | None. |
| | |
| | |
| | |
| | |
| | |

## *II.C Post-authorisation development plan*

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

There are no studies that are conditions of the marketing authorisation or specific obligation of Lytenava.

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

There are no studies in the post-authorisation development plan for Lytenava.

# Part VII: Annexes

## *Annex 4*

## *Specific adverse drug reaction follow-up forms*

### Endophthalmitis: follow-up questionnaire

| **1. Reporter Details** ☐Follow-up | | ☐Initial |
|---|---|---|
| Reporter Name: | | E-mail: |
| Contact address: | | Telephone number: |
| | | Fax number: |
| Type: | ☐ Physician (Specialty): _____ | ☐ Consumer or other non healthcare professional |
| | ☐ Pharmacist | ☐ Other (Specify) _____ |
| If reporter is a consumer, have they informed their physician of the exposure? ☐ Yes ☐ No<br>Has the consumer provided permission to contact their healthcare professional? ☐ Yes ☐ No | | |
| **If yes, please provide healthcare professional contact details:** | | |
| Name: | Type: | Telephone: |
| Address: | | Email: |

| **2. Patient Details** | | | | |
|---|---|---|---|---|
| Date of birth (Month/Year) | Age<br>yrs/mo. | Gender<br>☐ Male<br>☐ Female | Height<br>cm | Weight<br>kg |

| 3. Suspect Drug(s) Section | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Name | Strength | Dose | Route | Indication | Treatment start date (day/month/year) | Treatment end date (day/month/year) | Lot | Expiry |
| 1. | | | | | | | | | |
| 2. | | | | | | | | | |
| 3. | | | | | | | | | |
| 4. | | | | | | | | | |
| 5. | | | | | | | | | |

Was intravitreal bevacizumab (Lyteneva) administered in this patient? ☐ Yes ☐ No
If yes, were pre and perioperative antibiotic used before and during the procedure?
Were aseptic precautions taken during the procedure? ☐ Yes ☐ No

Which eye was the injection given in? ☐ Right ☐ Left ☐ Both.
Please provide relevant details of the procedure:

| 4. Concomitant Drug(s) Section | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Name | Strength | Dose | Route | Indication | Treatment start date (day/month/year) | Treatment end date (day/month/year) | Lot No : | Expiry Date |
| 1 | | | | | | | | | |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |

| 5. Other risk factors | |
|---|---|
| Did the patient have any of the following risk factors? | |
| ☐ any complications during the procedure | ☐ recent trauma to the eye |
| ☐ Trabeculectomy | ☐ glaucoma drainage procedures |
| ☐ Recent cataract surgery | ☐ IOL implantation |
| ☐ Phacoemulsification | ☐ posterior capsule rupture |
| ☐ Vitreoretinal procedures | ☐ lacrimal procedures |
| ☐ Infectious keratitis | ☐ Fungemia |
| ☐ Contact lens keratitis | ☐ Bacteraemia |
| ☐ Communication between the anterior and vitreous | ☐ eyelid procedures |
| ☐ Diabetes mellitus | ☐ LASIK |
| ☐ Immunodeficiency | ☐ Autoimmune disorder |
| ☐ Immunosuppressive treatment | |

| Please provide relevant details: |
|---|
| |

| **6. Symptoms of Endophthalmitis in the patient** | |
|---|---|
| Does the patient have any of the following symptoms? | |
| ☐ Eye pain | ☐ Red eye |
| ☐ decreased vision | ☐Sensitivity to light |
| ☐ Floaters | ☐ Swelling of eyelid |
| Other relevant symptoms: | |

| **7. History of Present Illness** |
|---|
| |
| Is the patient currently suffering from endophthalmitis? ☐ Yes ☐ No<br><br>Which eye is affected? ☐ Right ☐ Left ☐ Both.<br><br>If yes, which of the following type is it based on the mode of entry of organism? ☐ Exogenous ☐ Endogenous<br><br>Based on the aetiology, which of the following types is it most likely to be?<br>Post-traumatic endophthalmitis ☐<br>Acute postoperative endophthalmitis ☐<br>Chronic post-operative endophthalmitis ☐<br>Delayed onset endophthalmitis ☐<br>Post intravitreal injection endophthalmitis ☐<br>Endophthalmitis after infectious keratitis ☐<br>Endogenous endophthalmitis following bacteraemia or fungemia ☐ |

| **8. Details of the Event** | | | | | |
|---|---|---|---|---|---|
| Adverse Event | Start Date (day/month/year) | Stop Date (day/month/year) | Hospitalisation | Outcome | Is the endophthalmitis related to Lyteneva use? |
| | | | ☐ Yes | ☐ Recovered / Resolved | ☐ Related |

| | | | | | |
|---|---|---|---|---|---|
| | | | ☐ No<br>If yes, provide dates of hospitalization: | ☐ Recovered / Resolved with Sequelae<br>☐ Recovering/Resolving<br>☐ Not Recovered /Not Resolved<br>☐ Fatal<br>☐ Unknown | ☐ Not Related<br>☐ Unknown |

Duration of endophthalmitis ___ ☐ Days___ ☐ Months ___ ☐ Years ____ ☐ Not Applicable

Was the diagnosis confirmed? ☐ Yes ☐ No

**Action taken with Lyteneva in response to the event:**
☐ Drug withdrawn.
☐ Drug dose reduced.
☐ Drug dose increased.
☐ No change in dose
☐ Unknown.
☐ Not applicable.

Did the reaction recover on stopping the drug? ☐ Yes ☐ No
Was Lyteneva restarted in the patient after endophthalmitis resolved? ☐ Yes ☐ No
Did the reaction reappear after restarting Lyteneva? ☐ Yes ☐ No

## 9. Details of Examination

| Date | Please provide the following details if available: | Left Eye | Right eye | Comments |
|---|---|---|---|---|
| | Visual Acuity | | | |
| | Intraocular pressure | | | |
| | Lids/Adnexa | | | |
| | Cornea | | | |
| | Iris | | | |
| | Lens | | | |
| | Fundus | | | |
| | Fluorescein angiography | | | |
| | Optical Coherence Tomography | | | |
| | Culture results | | | |

| | | | | |
|---|---|---|---|---|
| | | | | |
| | Other Relevant Laboratory tests (including blood and radiology tests): | | | |

## 10. Management of Endophthalmitis

Treatment provided for endophthalmitis:

Does the patient have any of the following complications after recovery:

Pan ophthalmitis ☐
Glaucoma ☐
Orbital cellulitis ☐
Intracranial spread ☐
Septicaemia ☐
Loss of vision ☐
Phthisis ☐
Hypotony ☐
Painful blind eye ☐

Any other sequelae:

| **Completed By** | | |
|---|---|---|
| Name: | Signature: | Date (day/month/year): |

## Thromboembolic events in the eye(s): follow-up questionnaire

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

For cases reporting thromboembolic events in eye(s) (including ocular vasculitis, retinal vasculitis, necrotising retinitis, choroidal infarction, eye infarction, macular ischemia, ocular ischemic syndrome, retinal artery embolism, retinal artery occlusion, retinal artery stenosis, retinal artery thrombosis, retinal infarction, retinal ischemia, retinal vascular occlusion, retinal vascular thrombosis, retinal vein occlusion, and retinal vein thrombosis), please ask the following questions:

**Event Description**:

What were the presenting symptom(s) and diagnosis? (Specify if it was an intraocular inflammation with or without retinal vasculitis/ retinal vascular occlusion)

Symptoms: _____(dd/mmm/yyyy): _____/_____/_____

Diagnosis:_____(dd/mmm/yyyy): _____/_____/_____

Date of last Lytenava injection prior to the event: _____

Did the adverse event occur in the eye(s) injected with Lytenava?

☐ Yes ☐ No ☐ Unknown

Eye(s) affected: ☐ Right eye ☐ Left eye ☐ Both eyes ☐ Unknown

Eye(s) treated with Lytenava: ☐ Right eye ☐ Left eye ☐ Both eyes ☐ Unknown

Did the event cause significant vision loss/ decrease of Visual Acuity (VA)? ☐ Yes ☐ No ☐ Unknown

► If yes, please provide:

VA before event ____/_____ Snellen / LogMAR (please select) (dd/mmm/yyyy):____/_____/_____

VA at time of event ____/____ Snellen / LogMAR (please select) (dd/mmm/yyyy): _____/_____/_____

VA after event (if available) _____/____ Snellen / LogMAR (please select) (dd/mmm/yyyy): _____/_____/_____

What were the clinical features?

Anterior segment: _____

Posterior segment: _____

Is the intraocular inflammation

☐ non-infectious ☐ infectious

What tests were done?: _____

**Treatment of the event**

Please specify any treatment given (drug, dose and route of administration), duration of treatment:

| Drug | Dose | Route of administration/Duration of administration | Start date | Stop date |
|---|---|---|---|---|
| | | | | |
| | | | | |
| | | | | |

**Outcome of the event**

| Event | Outcome | | | | | |
|---|---|---|---|---|---|---|
| | Ongoing | Resolved | Resolved with sequelae, please specify | Improved | Deteriorated | Unknown |
| 1. | | | | | | |
| 2. | | | | | | |

Please provide the **number** of Lytenava injections received prior to the onset of the event (including most recent injection) (dd/mmm/yyyy): _____

Please enter calendar dates of Lytenava injections (at least **for the last 3 injections**) received prior to the onset of the event (including most recent injection) (dd/mmm/yyyy):

1. _____/_____/_____
2. _____/_____/_____
3. _____/_____/_____

Did the patient receive anti-VEGF intravitreal injections before starting Lytenava?

☐ Yes ☐ No ☐ Unknown

►If yes, what product and approximately how many injections.

_____

_____

Were any other medications administered via intravitreal injection prior to the event?

☐ Yes ☐ No ☐ Unknown

►If yes, please describe and provide the calendar dates of administration (dd/mmm/yyyy), including which eye(s) was treated

_____

_____

Please provide a description of findings on the retinal image taken. Please specify the modality:

_____

_____

_____

_____

**Details for specific events: vascular occlusion** *If vascular occlusion was not reported, move to next question*

Was the retinal vascular occlusion in an ☐ Artery or ☐ Vein

Was the retinal vascular occlusion ☐ Central ☐ Branch, or ☐ Peripheral

Please provide any other relevant details:

**Medical history and underlying disorders**

Did the patient have any of the following?

☐ Hypertension ☐ Myocardial infarction ☐ Stroke ☐ Cardiac arrhythmia

☐ Diabetes ☐ Smoking ☐ Metabolic syndrome (hyperlipidemia, hypertension and DM)

☐ Coagulation disorders (e..g., factor V Leiden mutation, Protein C or S deficiency hyperhomocysteinemia etc.)

☐ Glaucoma ☐ Hormonal contraception

☐ Auto-immune diseases, please specify:_____

☐ Other ocular diseases, please specify:_____

☐ Other, please specify:_____

☐ None ☐ Unknown

☐ Prior history of Intraocular inflammation (within 12 months before Lytenava treatment), please specify if known etiology, for example with other anti-VEGFs or treatments:

_____

_____

## *Annex 6*

## *Details of proposed additional risk minimisation activities (if applicable)*

Prior to the use of Lytenava in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at patients and care-givers to adequately informing patients/carers on the risks of Lytenava, the key signs and symptoms of those risks, and when to seek urgent attention from their physician with the objective to minimise the risks and any resultant complications by encouraging prompt intervention.

The MAH shall ensure that in each Member State where Lytenava is marketed, all healthcare professionals who are expected to treat patients with Lytenava have access to the following educational package:

- Patient information pack, including a patient/carer guide and patient information leaflet.

**Patient Information Pack**

A patient information pack consists of the patient information leaflet and a patient/care-giver guide. The patient guide includes the following key elements:

- A description of neovascular age-related macular degeneration (nAMD)
- A description of Lytenava, how it works, and what to expect from treatment with Lytenava
- A description of the key signs and symptoms of the key risks associated with Lytenava, like local eyes effects (i.e., infectious endophthalmitis, intraocular pressure increase, intraocular inflammation, retinal detachment and retinal tear) and thromboembolic events after intravitreal injection of bevacizumab
- A description of when to seek urgent attention from the health care provider should signs and symptoms of these risks present themselves.
- Recommendations for adequate care after the injection
- Provide detailed information on correct use of the product and warning to avoid the off label use in special population, including but not limited to children and adolescent under 18 years.

**PATIENT GUIDE**

**PrLYTENAVA**

Bevacizumab gamma

| |
|---|
| **Patient's Name:** |
| **Date Lyteneva was first prescribed (MM/DD/YYYY):** |
| **Healthcare Centre Name:** |
| **Treating Healthcare Practitioner's Name:** |

| **Treating Healthcare Practitioner's Phone Number:** |
| --- |
| **Contact information of Pharmacist:** |

## Neovascular age-related macular degeneration (nAMD)

Neovascular age-related macular degeneration (nAMD) is a common world-wide cause of visual loss. Age related macular degeneration is an eye disease which decreases the central vision due to age related damage to the macula which is the part of the retina that processes straight-ahead vison. Neovascular age-related macular degeneration (wet AMD) is an advanced type of AMD characterised by choroidal neovascularisation, in which newly created blood vessels leak into the retina, producing distortion and fast loss of vision. Vascular endothelial growth factor (VEGF) is a signal protein that stimulates the formation of blood vessels.

## Lyteneva (Bevacizumab gamma)

Lyteneva (Bevacizumab gamma) is a recombinant humanised monoclonal antibody specific for human vascular endothelial growth factor (VEGF). Bevacizumab gamma binds VEGF and prevents the interaction of VEGF to its receptors on the surface of endothelial cells. By inhibiting, bevacizumab gamma suppresses endothelial cells proliferation, neovascularisation, and vascular permeability. Inhibition of angiogenesis works to block the growth of abnormal blood vessels in the back of the eye.

Lytenava is administered directly into the vitreous to exert local effects in the eye. The recommended dose for Lytenava in adults is 1.25 mg administered as a single intravitreal injection every 4 weeks (monthly). This corresponds to an injection volume of 0.05 ml.

## Contraindications of Lyteneva

Lyteneva should not be administered if you have any of the following conditions:

- are allergic to bevacizumab gamma or any of the other ingredients of this medicine.
- have an infection in or around your eye.
- have an inflammation in your eye.

## Warnings

Talk to your doctor before using Lytenava if you have:

- an eye condition usually caused by high eye pressure called glaucoma.
- a sudden increase in the size and number of floaters (dark floating spots), or a history of seeing flashes of light or floaters.
- had eye surgery in the last 4 weeks or an eye surgery is planned in the next 4 weeks.
- ever had any eye diseases or eye treatments.
- had blood clots, had a heart attack or stroke, are known to have reduced blood flow to the heart, or have a previous history of heart disease.

Tell your doctor if you are using, have recently used or might use any other medicines.
Proper aseptic injection techniques should always be used when administering Lytenava Intravitreal injections have been associated with endophthalmitis and retinal detachments.

If you suffer from any of the following conditions after receiving Lyteneva contact your doctor without delay, to permit prompt and appropriate management should an infection occur.

- Eye pain
- loss of vision
- photophobia or sensitivity to light
- blurred or decreased vision.
- floaters or an increased number of small particles in their vision
- redness or discomfort in the eye

It is important to know:

- the safety and efficacy of Lytenava when administered to both eyes at the same time have not been studied and such use may increase the risk of side effects.
- Injections with Lytenava may cause a temporary increase in eye pressure within 60 minutes after injection. Your doctor will monitor this after each injection.
- your doctor will check whether you have other risk factors that increase the risk of a tear or detachment of one of the layers of the back of the eye.
- when medicines that work similarly to Lytenava are given, there is a risk of blood clots blocking blood vessels. This may lead to heart attack or stroke. As small amounts of the medicine enter the blood, there is a theoretical risk of such events following injection of Lytenava into the eye.

Children and adolescents under 18 years

- The use of Lytenava in children and adolescents has not been established and is therefore not recommended.

Pregnancy and breast-feeding

- Women who could become pregnant must use effective contraception during treatment and for at least three further months after the last injection of Lytenava.
- There is no experience of using Lytenava in pregnant women. Lytenava is not recommended during pregnancy unless the potential benefit outweighs the potential risk to the unborn child. If you are pregnant, think you may be pregnant or planning to become pregnant, discuss this with your doctor before treatment with Lytenava.
- Lytenava is not recommended during breast-feeding because it is not known whether Lytenava passes into human milk. Ask your doctor or pharmacist for advice before Lytenava treatment.

Driving and using machines

- After Lytenava treatment you may experience some temporary vision blurring. If this happens, do not drive, or use machines until it resolves.

## Side Effects

The side effects with Lytenava injection result from either the medicine itself or the injection procedure and mostly affect the eye.
Contact your doctor immediately if you have any of the following serious side effects:

- serious inflammation or infection inside the eye called endophthalmitis.
- seriously increased eye pressure.
- temporary blindness.

Symptoms of these serious side effects are pain or increased discomfort in your eye, worsening eye redness, blurred, or decreased vision, increased number of small particles in your vision or increased sensitivity to light.
Other possible side effects:
Common side effects (may affect up to 1 in 10 people)

- small particles or spots in your vision (floaters).
- eye pain.
- bleeding in the conjunctiva.
- increased eye pressure.

Uncommon side effects (may affect up to 1 in 100 people)

- detachment or tear of one of the layers in the back of the eye (retinal pigment epithelial tear, vitreous detachment).
- bleeding in the eye.
- inflammation of the iris, the coloured part of the eye.
- corneal scar.
- inflammation or damage to the eye cornea, the clear layer that covers the iris (keratopathy, punctate keratitis).
- perceived flashes of light in the field of vision.
- eye discomfort.
- scratched corneas.
- eye irritation.
- itching of the eye.
- dry eye.
- red eye.
- iodine allergy.

## Other sources of information

Detailed information on this medicine i available on the European Medicines Agency web site: http://www.ema.europa.eu.

*To access an audiovisual version of the patient guide please visit [web address TBC] or scan the QR code:*