ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Lytenava 25 mg/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 25 mg bevacizumab gamma*.

Each vial contains 7.5 mg of bevacizumab gamma in 0.3 mL solution. This provides a usable amount to deliver a single dose of 0.05 mL containing 1.25 mg bevacizumab gamma.

*Bevacizumab gamma is a humanised monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Colourless to slightly brown solution with a pH of 6.1 and an osmolality of 235 – 315 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lytenava is indicated in adults for treatment of neovascular (wet) age-related macular degeneration (nAMD).

4.2 Posology and method of administration

This medicinal product must be administered by a qualified healthcare professional, experienced in intravitreal injections.

Posology

The recommended dose is 1.25 mg administered by intravitreal injection every 4 weeks (monthly). This corresponds to an injection volume of 0.05 mL.

Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity, i.e., no change in visual acuity or in other signs and symptoms of the disease under continued treatment. The kinetics of bevacizumab gamma efficacy (see section 5.1) indicate that three or more consecutive monthly injections may be needed initially. Thereafter, the healthcare professional may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters.

Monitoring and treatment intervals should then be determined by the healthcare professional and should be based on disease activity, including clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography).

If visual and anatomical outcomes indicate that the patient is not benefiting from continued treatment, the medicinal product should be discontinued. Treatment should also be withheld if clinically indicated, (see section 4.4).

Special populations

Elderly
No dose adjustment is required in patients aged 65 years and older.

Renal impairment
Bevacizumab gamma has not been studied in patients with renal impairment. Available data do not suggest a need for a dose adjustment is required in patients with renal impairment.

Hepatic impairment
Bevacizumab gamma has not been studied in patients with hepatic impairment. Available data do not suggest a need for a dose adjustment is required in patients with hepatic impairment.

Paediatric population
There is no relevant use of Lytenava in the paediatric population for the treatment of nAMD.

Method of administration

The medicinal product is for intravitreal use only. Each vial should only be used for the treatment of a single eye.

Since the volume contained in the vial (0.3 mL) is greater than the recommended dose (0.05 mL), a portion of the volume contained in the vial must be discarded prior to administration.

Ensure that the injection is given immediately after preparation of the dose.

The intravitreal injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Sterile paracentesis equipment should be available as a precautionary measure. The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure (see section 4.4). Adequate anaesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection.

The injection needle should be inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 mL is then delivered slowly; a different scleral site should be used for subsequent injections.

For instructions on preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients with active or suspected ocular or periocular infections.

Active intraocular inflammation.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Intravitreal injection-related reactions

Intravitreal injections have been associated with endophthalmitis, intraocular inflammation and retinal detachments/tears (see section 4.8). Proper aseptic injection technique should always be used when administering the medicinal product.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available.
In addition, patients should be monitored following the injection to permit early treatment should an infection occur.

Patients should be instructed to report any symptoms, such as eye pain, loss of vision, photophobia, blurred vision, floaters, or redness, suggestive of endophthalmitis or any of the above-mentioned events without delay, to permit prompt and appropriate management.

Intraocular pressure increases

Increases in intraocular pressure have been noted post-injection (up to 60 minutes) while being treated with vascular endothelial growth factor (VEGF) inhibitors, including bevacizumab gamma (see section 4.8). Both intraocular pressure and the perfusion of the optic nerve head must be monitored prior to and following intravitreal injection with Lytenava and managed appropriately.

Special precaution is needed in patients with poorly controlled glaucoma (do not inject the medicinal product while the intraocular pressure is ≥30 mmHg).

Bilateral treatment

The safety and efficacy of bevacizumab gamma administered in both eyes concurrently have not been studied. If bilateral treatment is performed at the same time, this could lead to an increased potential for adverse events, both ocular and systemic due to increased exposure.

Immunogenicity

As this is a therapeutic protein, there is a potential for immunogenicity with bevacizumab gamma. Patients should be instructed to inform their physician if they develop symptoms 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.

Concomitant use of other anti-VEGF (vascular endothelial growth factor) medicinal products

There are no data available on the concomitant use of bevacizumab gamma with other anti-VEGF medicinal products in the same eye. Bevacizumab gamma should not be administered concurrently with other anti-VEGF medicinal products (systemic or ocular).

Withholding treatment

The dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of:

- a decrease in best-corrected visual acuity (BCVA) of ≥30 letters compared with the last assessment of visual acuity;
- a retinal break;
- a subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥50% of the total lesion area;
- an intraocular pressure of ≥30 mmHg
- thromboembolism, including myocardial infarction (MI), acute coronary syndrome (ACS), stroke, deep vein thrombosis (DVT), and pulmonary embolism (PE)
- performed or planned intraocular surgery within the previous or next 28 days.

Retinal pigment epithelial tear

Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for nAMD include a large and/or high pigment epithelial retinal detachment. When initiating bevacizumab gamma therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.

Rhegmatogenous retinal detachment or macular holes

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

Systemic effects following intravitreal use

Non-ocular haemorrhages and arterial thromboembolic events, have been reported following intravitreal injection of VEGF inhibitors, (see section 4.8). There are limited data on safety in the treatment of patients with nAMD with a history of stroke, transient ischaemic attacks or myocardial infarction within the last 3 months. Caution should be exercised when treating such patients.

Excipients with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Based on the elimination of bevacizumab, no interactions are expected. However, bevacizumab gamma should not be administered concurrently with other systemic or ocular anti-VEGF medicinal products (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment with bevacizumab gamma and for at least three months after the last dose when stopping treatment with bevacizumab gamma.

Pregnancy

There are no data on the use of bevacizumab gamma in pregnant women. Based on studies in animals with other anti-VEGFs, treatment with bevacizumab gamma may pose a risk to human embryo foetal development. Therefore, bevacizumab gamma should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.

Breast-feeding

There are no data available on the presence of bevacizumab gamma in human milk, the effects of bevacizumab gamma on the breast-fed infant or the effects of bevacizumab gamma on milk production/excretion. A risk to the breast-fed newborn/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to abstain from Lytenava therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No reproductive or fertility studies have been conducted with bevacizumab gamma. VEGF inhibition has been shown to affect follicular development, corpus luteum function and fertility (see section 5.3). Ovarian effects can be attributed to a direct result of the local inhibition of VEGF on active angiogenesis, which is profound in the ovary.

4.7 Effects on ability to drive and use machines

Lytenava has a minor influence on the ability to drive and use machines due to possible temporary visual disturbances following the intravitreal injection and the associated eye examination. Patients should not drive or use machines until these temporary visual disturbances subside.

4.8 Undesirable effects

Summary of the safety profile

The majority of adverse reactions reported following administration of bevacizumab gamma are related to the intravitreal injection procedure. The most frequently reported adverse reactions were conjunctival haemorrhage (5.0%), vitreous floaters (1.5%), eye pain (1.2%), and intraocular pressure increased (1.2%). Less frequently reported, but more serious adverse reactions were intraocular pressure increases (0.6%), blindness transient (0.3%), endophthalmitis (0.3%), intraocular inflammation (0.3%).

Tabulated list of adverse reactions

A total of 341 patients from two randomized and one open-label clinical studies were treated with the recommended dose of 1.25 mg. The adverse reactions reported in clinical studies of bevacizumab gamma are listed in Table 1 below.

Adverse reactions are listed according to the MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Frequency categories for each adverse reaction are based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Frequencies of adverse reactions

System organ class	Common	Uncommon
Infections and infestations		Endophthalmitis
Immune system disorders		Iodine allergy
Eye disorders	Vitreous floaters Eye pain Conjunctival haemorrhage	Retinal pigment epithelial tear, Vitreous haemorrhage, Iritis, Corneal scar, Keratopathy, Punctate keratitis, Blindness transient, Vitreous detachment, Photopsia, Ocular discomfort, Corneal abrasion, Eye irritation, Eye pruritus, Dry eye, Ocular hyperaemia
Investigations	Intraocular pressure increased	

Description of selected adverse reactions

Product-class-related adverse reactions
There is a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors. A low incidence rate of arterial thromboembolic events was observed in the bevacizumab gamma clinical studies in patients with nAMD (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdosing with greater than recommended injection volume may increase intraocular pressure. In the event of overdose, intraocular pressure should therefore be monitored and, if deemed necessary by the treating healthcare professional, appropriate treatment should be initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmolgicals, antineovascularisation agents, ATC code: S01LA08

Mechanism of action

Bevacizumab gamma is a recombinant humanised IgG1 monoclonal antibody (mAb) for human vascular endothelial growth factor (VEGF).

Bevacizumab gamma binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. Bevacizumab gamma is a human VEGF inhibitor that binds to all isoforms of VEGF-A, thereby preventing interaction with receptors VEGFR-1 and VEGFR-2. By inhibiting VEGF-A, bevacizumab gamma suppresses endothelial cells proliferation, neovascularization, and vascular permeability. Inhibition of angiogenesis works to block the growth of abnormal blood vessels in the back of the eye.

Pharmacodynamic effects

Neovascular AMD
In the NORSE TWO study, anatomical parameters related to leakage of blood and fluid that characterise choroidal neovascularisation (CNV) were part of the disease activity assessments. A mean decrease in central retinal thickness (CRT) of 119.7 microns at month 11 compared to baseline was observed in patients receiving monthly 1.25 mg bevacizumab gamma intravitreal injections.

Immunogenicity
No evidence of anti-drug antibodies (ADA) impact on pharmacokinetics, efficacy or safety was observed, however, data are still limited.

Clinical efficacy and safety

The efficacy and safety of bevacizumab gamma was assessed in two randomised, multicentre, double-masked, active controlled Phase III studies (NORSE ONE and NORSE TWO) in patients with nAMD. In NORSE ONE, both patients with previously treated and treatment naive study eyes were enrolled and a total of 61 patients were randomized 1:1 (31 subjects in the bevacizumab group and 30 subjects in the ranibizumab group). Patient ages ranged from 61 to 97 years, with a mean age of 79 years; 97% of patients were over 65 years. In NORSE TWO, treatment naive study eyes were enrolled and a total of 228 patients were randomised 1:1 (113 subjects in the bevacizumab gamma group and 115 subjects in the ranibizumab group). Patient ages ranged from 54 to 98 years, with a mean age of 79 years; 95% of patients were over 65 years.

In both studies, patients randomised to receive bevacizumab gamma were administered at a dose of 1.25 mg by intravitreal injection in the study eye every month for 12 months. Patients randomised to ranibizumab control were administered at a dose of 0.5 mg by intravitreal injection in the study eye every month for 3 months (i.e. on Days 0, 30, and 60) followed by every 90 days (i.e. on Days 150 and 240), which was a sublabel dosing regimen. In total, 5 injections in the ranibizumab arm were compared to 11 injections in the bevacizumab gamma arm for the assessment of the primary endpoint. The primary endpoint was assessed at the Month 11 visit, which was approximately 30 days after the last bevacizumab gamma dose and 90 days after the last ranibizumab dose.

The primary endpoint in both studies was the proportion of subjects who gained ≥15 letters in best corrected visual acuity (BCVA) from baseline to month 11, as measured by the early treatment diabetic retinopathy study (ETDRS) letter score, with the primary objective being to demonstrate the efficacy of bevacizumab gamma in a nAMD population. Secondary endpoints evaluated the change from baseline at month 11 in mean BCVA and the proportion of subjects who lost fewer than 15 letters in BCVA.

Results
The proportion of subjects in the NORSE ONE study who achieved an increase of ≥15 letters in BCVA from baseline to 11 months was 7.7% vs 20.8%, respectively, in the bevacizumab gamma and ranibizumab groups, (risk difference of 13.14% [95% CI = −35.50%, 7.65%]).Based on the primary endpoint the NORSE ONE study failed to demonstrate superiority of bevacizumab gamma over ranibizumab.

The NORSE TWO study met its primary efficacy endpoint and bevacizumab gamma demonstrated efficacy. The proportion of subjects who achieved an increase of ≥15 letters in BCVA from baseline to 11 months was 41.7% and 23.1% respectively, in the bevacizumab gamma and ranibizumab groups

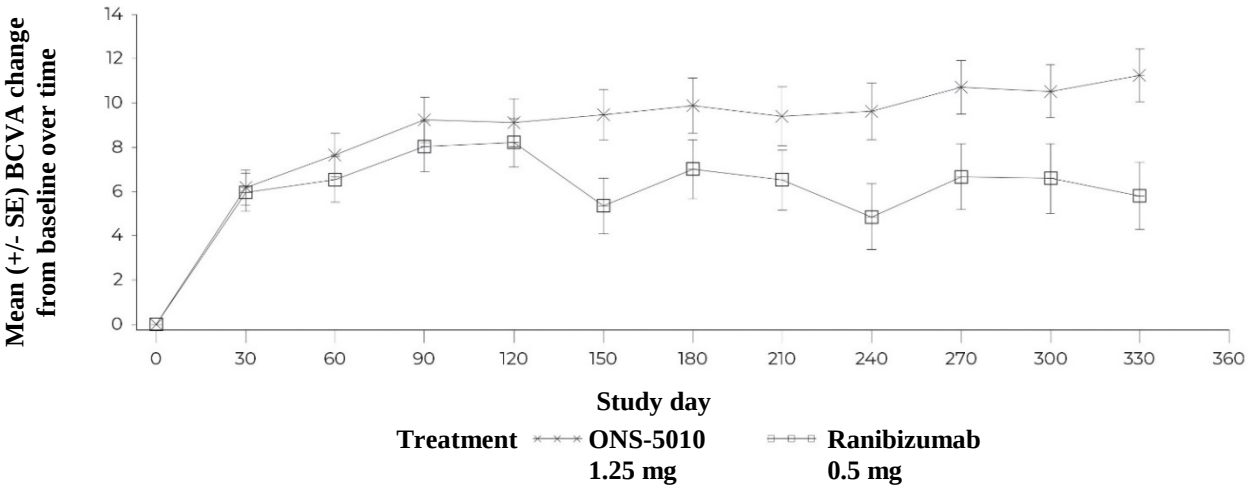
(risk difference of 18.59% [95% CI = 4.42%, 30.86%]). The primary efficacy analysis was statistically significant, in favour of bevacizumab gamma.

The efficacy of bevacizumab gamma was further supported when evaluating the change from baseline to month 11 in mean BCVA. The difference between the treatments and its corresponding 95% CI was 3.805 (-0.016, 7.626) BCVA letters.

Table 2 NORSE TWO primary and secondary efficacy endpoints – responder analysis

	Ranibizumab (N = 115)	**Bevacizumab gamma (N = 113)**
Primary Endpoint		
Subjects gaining ≥15 letters from baseline at 11 months, n/N (%)	24/104 (23.1)	45/108 (41.7)
Risk difference		18.59%
95% CI		4.42%; 30.86%
Secondary Endpoints		
BCVA mean change from baseline to 11 months, mean (SD)	5.8 (14.80)	11.2 (12.19)
LS mean change difference		3.805
95% CI		-0.016, 7.626
Subjects gaining ≥10 letters from baseline at 11 months, n/N (%)	36/104 (34.6)	61/108 (56.5)
Risk difference		21.87%
95% CI		7.26%, 34.87%
Subjects gaining ≥5 letters from baseline at 11 months, n/N (%)	53/104 (51.0)	74/108 (68.5)
Risk difference		17.56%
95% CI		3.15%, 30.52%
Subjects losing <15 letters from baseline at 11 months, n/N (%)	86/104 (82.7)	101/108 (93.5)
Risk difference		10.83%
95% CI		1.68%, 20.44%

Figure 1 NORSE TWO - Best-corrected visual acuity change from baseline over time*



*ONS-5010 (bevacizumab gamma) was dosed monthly for 12 months; ranibizumab was dosed every month for 3 months (i.e. on Days 0, 30, and 60) followed by every 90 days (i.e. on Days 150 and 240). In total, 5 injections in the ranibizumab arm were compared to 11 injections in the ONS-5010 arm for the assessment of the efficacy endpoints.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with bevacizumab gamma in all subsets of the paediatric population in neovascular AMD (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Bevacizumab gamma is administered intravitreally to exert local effects in the eye.

Following a single dose of 2 mg/kg intravenous infusion of bevacizumab gamma in 45 healthy male volunteers, the peak concentration was reached at 2 hours. The geometric mean C_{max} and total exposure (AUC_{0-t}) values were 40 µg/mL and 12 148 h•µg/mL, respectively.

In general, the serum PK following intravitreal administration of bevacizumab gamma, was significantly lower than that seen following intravenous administration. No PK parameters could be characterised from the generated clinical data.

5.3 Preclinical safety data

In a review of the preclinical safety evaluation of bevacizumab, female cynomolgus monkeys administered intravenous bevacizumab twice weekly for 13 weeks had decreased ovarian weight and a microscopic correlate of absence of corpora lutea at ≥10 mg/kg that was reversible after a 4-week recovery period. Ovarian effects can be attributed to a direct result of the local inhibition of VEGF on active angiogenesis, which is profound in the ovary.

No carcinogenicity or mutagenicity data are available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate monohydrate
Disodium hydrogen phosphate
α,α-Trehalose dihydrate
Polysorbate 20 (E432)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
The unopened vial may be stored outside the refrigerator below 25 °C for up to 12 hours.

6.5 Nature and contents of container

Lytenava 25 mg/mL solution for injection contains 0.3 mL solution in a 2 mL vial (Type 1 glass) with a stopper (butyl rubber) containing 7.5 mg of bevacizumab gamma.

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

The solution should be inspected visually upon removal from the refrigerator and prior to administration. If particulates or cloudiness are visible, the vial must not be used, and appropriate replacement procedures must be followed.

The content of the vial is sterile and for single use only. Do not use if the packaging or vial are damaged or expired.

The vial contains more than the recommended dose of 1.25 mg. Injecting the entire volume of the vial could result in overdose. The excess medicinal product and any air bubbles should be carefully expelled from the syringe prior to injection. The injection dose must be set to the 0.05 mL dose mark (1.25 mg bevaiczumab gamma). Ensure that the injection is given immediately after preparation of the dose.

Use aseptic technique to carry out the following preparation steps:

1. Prepare for intravitreal injection with the following recommended commercially available medical devices for single use (not provided):
    - 5 micron sterile filter needle, 18-gauge × 1½ inch (micro acrylic copolymer filter; polycarbonate/stainless steel 304 needle or equivalent)
    - 1 mL sterile silicone-free syringe with marking to measure 0.05 mL (polypropylene/polyethylene or equivalent)
    - Sterile injection needle, 30-gauge × ½ inch (polypropylene/stainless steel or equivalent)
    - Alcohol swab

2. Before withdrawal, disinfect the outer part of the rubber stopper of the vial.
3. Place the 5 micron filter needle onto the 1 mL syringe using aseptic technique.
4. Push the filter needle into the centre of the vial stopper and ensure the tip of the needle remains within the Lytenava solution to minimise the potential for air bubbles.
5. Withdraw the contents of Lytenava to ensure a full dose can be prepared in the syringe, keeping the vial in an upright position, slightly inclined to ease sufficient withdrawal.
6. Ensure that the plunger rod is drawn sufficiently back when drawing up Lytenava to provide for sufficient volume to prepare a 0.05 mL injection.
7. The filter needle should be discarded after withdrawal of the vial content and must not be used for the intravitreal injection.
8. Attach a 30-gauge × ½ inch sterile injection needle firmly onto the syringe by screwing it tightly onto the syringe hub. Carefully remove the needle cap by pulling it straight off. Do not wipe the needle at any time.
9. Hold the syringe with the needle pointing up. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top.
10. Hold the syringe at eye level and carefully push the plunger rod until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Outlook Therapeutics Limited
10 Earlsfort Terrace
Dublin 2
D02 T380
Ireland

8. MARKETING AUTHORISATION NUMBER

EU/1/24/1798/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 May 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

FUJIFILM Diosynth Biotechnologies Texas, LLC
3939 Biomedical Way
College Station, Texas (TX) 77845
United States (USA)

Name and address of the manufacturer responsible for batch release

MIAS Pharma Limited
Suite 1, Stafford House, Strand Road
Portmarnock
Dublin
D13 WC83
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Lytenava in each Member State, the Marketing Authorisation Holder (MAH) must agree with the National Competent Authority on the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme.
The educational programme is aimed at adequately informing patients/care-givers on the risks of Lytenava, the key signs and symptoms of those risks, and when to seek urgent attention from their physician. The objective of the educational programme is to minimize the risks and any resultant complications by encouraging prompt intervention.
The MAH shall ensure that in each Member State where Lytenava is marketed, all patients and their care-givers, who are expected to be exposed to Lytenava, have access to/are provided with the following educational package:

- Patient information pack

The patient information pack consists of the patient information leaflet and a patient/care-giver guide. The patient guide is provided in written and audio format, and will include 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, i.e. infectious endophthalmitis
- 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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lytenava 25 mg/mL solution for injection
bevacizumab gamma

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One mL contains 25 mg of bevaziumab gamma. Each vial contains 7.5 mg bevacizumab gamma in 0.3 mL solution.

3. LIST OF EXCIPIENTS

Excipients: α, α-trehalose dihydrate, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate, polysorbate 20 (E432), water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 × 0.3 mL vial
7.5 mg/0.3 mL
Single dose: 1.25 mg/0.05 mL. Excess volume to be expelled.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravitreal use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.

Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Outlook Therapeutics Limited
10 Earlsfort Terrace
Dublin 2
D02 T380
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1798/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Lytenava 25 mg/mL injection
bevacizumab gamma
Intravitreal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

7.5 mg/0.3 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Lytenava 25 mg/mL solution for injection
bevacizumab gamma

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lytenava is and what it is used for

What Lytenava is
Lytenava contains the active substance bevacizumab gamma, which belongs to a group of medicines called antineovascularisation agents.

What Lytenava is used for
Lytenava is used in adults to treat an eye condition called neovascular (wet) age-related macular degeneration (nAMD).
This eye condition is characterised by the abnormal formation and growth of blood vessels underneath the macula. The macula is the central part of the retina at the back of the eye and is responsible for clear vision. The abnormal growth and formation of blood vessels may leak fluid or blood into the eye and interfere with the macula's function.

How Lytenava works
Lytenava specifically binds to a protein called human vascular endothelial growth factor A (VEGF-A), which is present in the eye. In excess, this growth factor causes abnormal growth of blood vessels in the eye, which can reduce vision. By binding to this growth factor, Lytenava can block its actions and prevent abnormal growth. This can help to stabilise or improve your vision.

2. What you need to know before you use Lytenava

You must not receive Lytenava if you
- are allergic to bevacizumab gamma or any of the other ingredients of this medicine (listed in section 6)
- have an infection in or around your eye
- have an inflammation in your eye

Tell your doctor if any of these apply to you.

Warnings and precautions
Talk to your doctor before using Lytenava if you have:
- glaucoma, an eye condition usually caused by high eye pressure
- a history of seeing flashes of light or floater or a sudden increase in the size and number of floaters (small, dark shapes moving in the field of vision)
- had blocked blood vessels, caused by a blood clot, such as heart attack, stroke, blood clots formed in the deep veins of the legs or lungs
- 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

Tell your doctor immediately if you have:
- sudden vision loss
- signs of an eye infection or inflammation, such as
  - worsening of eye redness or increased eye discomfort
  - increased number of floaters in your vision or sensitivity to light
  - eye pain
  - blurred or decreased vision

It is important to know:
- safety and efficacy of Lytenava given to both eyes at the same time has not been studied. Such use may increase 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 for factors increasing risk of a tear or detachment of one of the layers at back of the eye

When some other medicines that work in a similar way to Lytenava are given, there is a risk for the formation of blood clots that can block 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.

Please see section 4 (“Possible side effects”) for more detailed information on side effects that could occur during Lytenava therapy.

Children and adolescents under 18 years
The use of Lytenava in children and adolescents has not been established and is therefore not recommended.

Other medicines and Lytenava
Tell your doctor if you are using, have recently used, or might use any other medicines.

Pregnancy and breast-feeding
- Women who could become pregnant must use effective contraception during treatment and for at least three months after the last injection of Lytenava.
- There is no experience of using bevacizumab gamma 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 starting treatment with Lytenava.
- Lytenava is not recommended during breast-feeding because it is not known whether bevacizumab gamma passes into breast 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 this resolves.

Lytenava contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to use Lytenava

Lytenava is given as a single injection into your eye by your doctor. The usual dose of an injection is 0.05 mL (which contains 1.25 mg of bevacizumab gamma). The interval between two doses injected into the same eye should be about four weeks.

Before the injection, your doctor will wash your eye carefully to prevent infection. Your doctor will also give you a local anaesthetic to reduce or prevent any pain you might have with the injection.

The treatment starts with one injection of Lytenava every 4 weeks. After the first few treatments (about 3), your doctor will determine the frequency of further treatments by monitoring the condition of your eye, such as your vision and the health of your eye. .

How long does Lytenava treatment last for
This is a long-term treatment, possibly continuing for months or years. Your doctor will check that the treatment is working during your regular scheduled visits. Your doctor may also check on your eyes between injections. If you have questions about how long you will receive Lytenava, talk to your doctor.

If you miss a dose of Lytenava
If you miss a dose, schedule a new appointment with your doctor as soon as possible.

Before stopping Lytenava treatment
If you are considering stopping Lytenava treatment, please go to your next appointment and discuss this with your doctor. Your doctor will advise you and decide how long you should be treated with Lytenava. Stopping treatment may increase your risk of vision loss and your vision may worsen.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects of 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:
- increased eye pressure that requires immediate intervention (uncommon, may affect up to 1 in 100 people)
- serious inflammation inside the eye often caused by infections, called endophthalmitis, or (uncommon, may affect up to 1 in 100 people)
- temporary blindness (uncommon, may affect up to 1 in 100 people)

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 are:
Common (may affect up to 1 in 10 people)
- small particles or spots in your vision (vitreous floaters)
- eye pain
- bleeding in the protective layer covering the eye called conjunctiva (conjunctival haemorrhage)

- increased eye pressure

Uncommon (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 (iritis)
- corneal scar
- inflammation or damage to the cornea, the clear layer covering the iris (keratopathy, punctate keratitis)
- perceived flashes of light in the field of vision (photopsia)
- eye discomfort
- scratching of the cornea (corneal abrasion)
- eye irritation
- itching of the eye (eye pruritus)
- dry eye
- red eye (ocular hyperaemia)
- iodine allergy

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Lytenava

Your doctor, pharmacist, or nurse is responsible for storing this medicine and disposing of any unused product correctly. The following information is intended for healthcare professionals.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze.
The unopened vial may be stored outside the refrigerator below 25 °C for up to 12 hours.

Keep the vial in the outer carton in order to protect from light.

6. Contents of the pack and other information

What Lytenava contains
- The active substance is bevacizumab gamma. Each mL contains 25 mg bevacizumab gamma. Each vial contains 7.5 mg of bevacizumab gamma in 0.3 mL solution. This provides a suitable amount to deliver a single dose of 0.05 mL containing 1.25 mg bevacizumab gamma.
- The other ingredients are sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate, α,α-trehalose dihydrate, polysorbate 20 (E432), water for injections.

What Lytenava looks like and contents of the pack
Lytenava 25 mg/mL solution for injection (injection) is colourless to slightly brown.

Pack containing one glass vial with butyl rubber stopper. The vial is for single use only.

Marketing Authorisation Holder and Manufacturer
Outlook Therapeutics Limited
10 Earlsfort Terrace
Dublin 2
D02 T380
Dublin
Ireland

Manufacturer
MIAS Pharma Limited
Suite 1, Stafford House, Strand Rd
Portmarnock
Dublin
D13 WC83
Ireland

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

The solution should be inspected visually upon removal from the refrigerator and prior to administration. If particulates or cloudiness are visible, the vial must not be used and appropriate replacement procedures must be followed.

The content of the vial is sterile and for single use only. Do not use if the packaging or vial are damaged or expired.

The vial contains more than the recommended dose of 1.25 mg. Injecting the entire volume of the vial could result in overdose. The excess medicinal product and any air bubbles should be carefully expelled from the syringe prior to injection. The injection dose must be set to the 0.05 mL dose mark (1.25 mg bevaiczumab gamma).

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Method of administration
Lytenava is provided in a single-use vial for intravitreal use only. Each vial should only be used for the treatment of a single eye.

Use aseptic technique to carry out the following preparation steps:
1. Prepare for intravitreal injection with the following recommended commercially available medical devices for single use (not provided):
    - 5 micron sterile filter needle, 18-gauge × 1½ inch (micro acrylic copolymer filter; polycarbonate/stainless steel 304 needle or equivalent)
    - 1 mL sterile silicone-free syringe with marking to measure 0.05 mL (polypropylene/polyethylene or equivalent)
    - Sterile injection needle, 30-gauge × ½ inch (polypropylene/ stainless steel or equivalent)
    - Alcohol swab
2. Before withdrawal, disinfect the outer part of the rubber stopper of the vial.
3. Place the 5 micron filter needle onto the 1 mL syringe using aseptic technique.

4. Push the filter needle into the centre of the vial stopper and ensure the tip of the needle remains within the Lytenava solution to minimise the potential for air bubbles.
5. Withdraw the entire content of Lytenava to ensure a full dose can be prepared in the syringe, keeping the vial in an upright position, slightly inclined to ease sufficient withdrawal.
6. Ensure that the plunger rod is drawn sufficiently back when drawing up Lytenava to provide for sufficient volume to prepare a 0.05 mL injection.
7. The filter needle should be discarded after withdrawal of the vial content and must not be used for the intravitreal injection.
8. Attach a 30-gauge × ½ inch sterile injection needle firmly onto the syringe by screwing it tightly onto the syringe hub. Carefully remove the needle cap by pulling it straight off. Do not wipe the needle at any time.
9. Hold the syringe with the needle pointing up. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top.
10. Hold the syringe at eye level and carefully push the plunger rod until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.

The intravitreal injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Sterile paracentesis equipment should be available as a precautionary measure. The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure. Adequate anaesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection.

The injection needle should be inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 mL is then delivered slowly; a different scleral site should be used for subsequent injections.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay.