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.

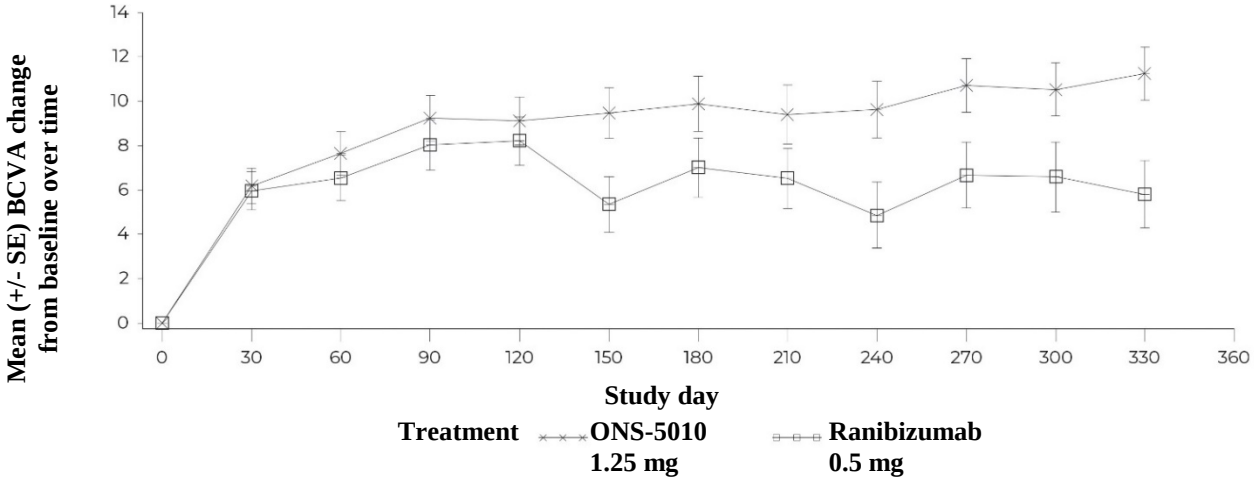
The efficacy of bevacizumab gamma was further supported when evaluating the change from baseline to month 11 in mean BCVA. The difference between the treatments and its corresponding 95% CI was 3.805 (-0.016, 7.626) BCVA letters.

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)

	Ranibizumab (N = 115)	Bevacizumab gamma (N = 113)
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

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 NL B.V.

Strawinskylaan 569

1077XX Amsterdam

The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PL 61807/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/07/2024

10 DATE OF REVISION OF THE TEXT

30/04/2026