SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Doxazosine Syri Pharma 0,4 mg/ml, suspensie voor oraal gebruik

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral suspension contains 0.4 mg of Doxazosin (as mesilate).

Excipient with known effect
Each ml of oral solution contains 1.8 mg methyl parahydroxybenzoate (E218), 0.2 mg propyl parahydroxybenzoate (E216) and 0.99 mg propylene glycol (E1520), 0.011 mg benzoic acid and 0.1574 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension
Lemon flavoured white to off-white coloured suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension:
Doxazosine Syri Pharma is indicated for the treatment of hypertension and can be used as a sole agent to control blood pressure in hypertensive patients.

In patients inadequately controlled on single antihypertensive therapy, Doxazosin may be used in combination with a thiazide diuretic, beta-adrenoceptor blocking agent, calcium antagonist or an angiotensin-converting enzyme inhibitor.

Benign Prostatic Hyperplasia:
Doxazosine Syri Pharma is indicated as an adjunct in the treatment of urinary outflow obstruction and symptoms associated with benign prostatic hyperplasia (BPH). It may therefore be of value in patients awaiting prostatic surgery or for whom surgery is not possible.

Doxazosine Syri Pharma may be used in BPH patients who are either hypertensive or normotensive.

4.2 Posology and method of administration

Posology
Adults: Doxazosine Syri Pharma is used in a once daily regimen and may be administered in the morning or evening.

Hypertension:
It is recommended that therapy be initiated at 1 mg (2.5 ml) given once daily for one or two weeks to minimise the potential for postural hypotension and/or syncope (see section 4.4). The dosage may then be increased to 2 mg (5 ml) once daily for an additional one or two weeks. If necessary the daily dosage should then be increased gradually at similar intervals to 4 mg (10

ml), 8 mg (20 ml), and l6 mg (40 ml) as determined by patient response to achieve the desired reduction in blood pressure. The usual dose is 2-4 mg (5-10 ml) once daily.
The maximum daily dose should not exceed 16 mg (40 ml).

Diuretic therapy may be introduced, if required.

Benign prostatic hyperplasia:
The recommended initial dosage of Doxazosine Syri Pharma is 1 mg (2.5 ml) given once daily to minimise the potential for postural hypotension and/or syncope (see section 4.4). Depending on the individual patient's urodynamics and BPH symptomatology, dosage may then be increased to 2 mg (5 ml) and thereafter to 4 mg (10 ml) and up to the maximum recommended dose of 8 mg (20 ml). The recommended titration interval is 1-2 weeks. The usual recommended dose is 2-4 mg (5-10 ml) once daily.

Paediatric population:
The safety and efficacy of Doxazosin in children and adolescents have not been established.

Elderly patients:
Normal adult dosage. In common with other drugs of this class, dosage should be kept as low as possible and increments made under close supervision.

Patients with renal impairment:
Since there is no change in pharmacokinetics in patients with impaired renal function the usual adult dose of Doxazosin is recommended. Doxazosin is not dialysable.

Patients with hepatic impairment:
There are only limited data in patients with liver impairment and on the effect of drugs known to influence hepatic metabolism (e.g. cimetidine). As with any drug wholly metabolised by the liver, Doxazosin should be used with care in patients with significant existing hepatic dysfunction (see section 4.4 and section 5.2).

Method of Administration
Oral administration.
Shake the suspension at least 30 seconds prior to prepare the dose.
Doses of 10 ml or below should be administered using the 10ml syringe. For doses greater than 10ml, the 20 ml syringe should be used.
Wash the syringe with water.

4.3 Contraindications

Doxazosin is contraindicated in:

- Hypersensitivity to the active substance, other types of quinazolines (e.g. prazosin, terazosin), or to any of the excipients listed in section 6.1
- Patients with a history of orthostatic hypotension
- Patients with benign prostatic hyperplasia and concomitant congestion of the upper urinary tract, chronic urinary tract infection or bladder stones
- Patients with hypotension (for benign prostatic hyperplasia indication only)

Doxazosin is contraindicated as monotherapy in patients with either overflow bladder or anuria with or without progressive renal insufficiency.

4.4 Special warnings and precautions for use

Postural Hypotension/Syncope:

Initiation of Therapy – In relation with the alpha-blocking properties of doxazosin, patients may experience postural hypotension evidenced by dizziness and weakness, or rarely loss of consciousness (syncope), particularly with the commencement of therapy (see section 4.2). Therefore, it is prudent medical practice to monitor blood pressure on initiation of therapy to minimise the potential for postural effects.

When instituting therapy with any effective alpha-blocker, the patient should be advised how to avoid symptoms resulting from postural hypotension and what measures to take should they develop. The patient should be cautioned to avoid situations where injury could result, should dizziness or weakness occur during the initiation of Doxazosin therapy, such as driving or operating machinery.

Use in patients with Acute Cardiac Conditions:

As with any other vasodilatory anti-hypertensive agent it is prudent medical practice to advise caution when administering doxazosin to patients with the following acute cardiac conditions:

- pulmonary oedema due to aortic or mitral stenosis
- heart failure at high output
- right-sided heart failure due to pulmonary embolism or pericardial effusion
- left ventricular heart failure with low filling pressure.

Use in Hepatically Impaired Patients:

There are only limited data in patients with liver impairment and on the effect of drugs known to influence hepatic metabolism (e.g. cimetidine). As with any drug wholly metabolised by the liver, Doxazosin should be administered with particular caution to patients with evidence of impaired hepatic function (see section 4.2 and section 5.2).
Since there is no clinical experience in patients with severe hepatic impairment use in these patients is not recommended.

Use with PDE-5 Inhibitors:
Concomitant administration of doxazosin with phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, and vardenafil) should be done with caution as both drugs have vasodilating effects and may lead to symptomatic hypotension in some patients. To reduce the risk of orthostatic hypotension it is recommended to initiate the treatment with phosphodiesterase-5-inhibitors only if the patient is hemodynamically stabilized on alpha-blocker therapy. Furthermore, it is recommended to initiate
phosphodiesterase-5-inhibitor treatment with the lowest possible dose and to respect a 6-hour time interval from intake of doxazosin. No studies have been conducted with doxazosin prolonged release formulations.

Use in patients with Renal Impairment:

There is no evidence that Doxazosin aggravates renal dysfunction. However, Doxazosin dosage introduction and adjustment should be carried out with great care.

Use in patients undergoing cataract surgery:

The 'Intraoperative Floppy Iris Syndrome' (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with tamsulosin. Isolated reports have also been received with other alpha-1 blockers and the possibility of a

class effect cannot be excluded. As IFIS may lead to increased procedural complications during the cataract operation current or past use of alpha-1 blockers should be made known to the ophthalmic surgeon in advance of surgery.

The mean terminal half-life of doxazosin is 22 hours. This may be prolonged in patients with congestive heart failure. The rate of dose adjustment may need to be slowed.
In some patients with left ventricular failure, the decrease in left ventricular filling associated with vigorous therapy may result in a significant fall in cardiac output and systemic blood pressure after administration of doxazosin. These effects should be kept in mind when introducing therapy and continuous adjustment of dose used.

Priapism:

Prolonged erections and priapism have been reported with alpha-1 blockers including doxazosin in post marketing experience. If priapism is not treated immediately, it could result in penile tissue damage and permanent loss of potency, therefore the patient should seek immediate medical assistance.
Screening for Prostate Cancer: Carcinoma of the prostate causes many of the symptoms associated with BPH and the two disorders can co-exist. Carcinoma of the prostate should therefore be ruled out prior to commencing therapy with doxazosin for treatment of BPH symptoms.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

Excipient warning:
Sodium: This medicinal product contains less than 1 mmol (23 mg) sodium per 5 ml, that is to say essentially 'sodium free'.

Methyl parahydroxybenzoate (E218) and Propyl parahydroxybenzoate (E216): may cause allergic reactions (possibly delayed).

Propylene glycol (E1520): This medicine contains 4.95 mg propylene glycol in each 5 ml dose which is equivalent to 0.99 mg/ml

Benzoic acid (E210): This medicinal product contains 0.055 mg benzoic acid in each 5 ml dose which is equivalent to 0.011 mg/ml.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of an alpha blocker with a PDE-5 inhibitor may lead to symptomatic hypotension in some patients (see section 4.4). No studies have been conducted with doxazosin prolonged release formulations.

Doxazosin is highly bound to plasma proteins (98%). *In vitro* data in human plasma indicates that doxazosin has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin or indometacin), however, the theoretical potential for interaction with other protein bound drugs should be borne in mind.

In vitro studies suggest that doxazosin is a substrate of cytochrome P450 3A4 (CYP 3A4). Caution should be exercised when concomitantly administering doxazosin with a strong CYP 3A4 inhibitor, such as clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, or voriconazole (see section 5.2).

Conventional doxazosin has been administered without any adverse drug interaction in clinical experience with thiazide diuretics, furosemide, beta-blockers, non-steroidal anti-inflammatory

drugs, antibiotics, oral hypoglycaemic drugs, uricosuric agents, and anticoagulants. However, data from formal drug/drug interaction studies are not present. Doxazosin potentiates the blood pressure lowering activity of other alpha-blockers and other antihypertensives.

In an open-label, randomized, placebo-controlled trial in 22 healthy male volunteers, the administration of a single 1 mg dose of doxazosin on day 1 of a four-day regimen of oral cimetidine (400 mg twice daily) resulted in a 10% increase in mean AUC of doxazosin, and no statistically significant changes in mean Cmax and mean half-life of doxazosin. The 10% increase in the mean AUC for doxazosin with cimetidine is within intersubject variation (27%) of the mean AUC for doxazosin with placebo.

4.6 Fertility, pregnancy and lactation

For the hypertension indication:

Pregnancy
There are no or limited amount of data from the use of Doxazosin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant dose levels (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Doxazosin during pregnancy.

Lactation
Doxazosin/metabolites have been identified in breastfed newborns/infants of a treated mother in minimal amount (see section 5.3). The effect of Doxazosin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Doxazosin therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
There are no data on the effects of Doxazosin on human fertility. Animal studies have shown adverse effects on sexual maturation as well as reduced copulation frequency and pregnancy rate. The clinical relevance of these findings is unknown.

For the benign prostatic hyperplasia indication:

Fertility
There are no data on the effects of Doxazosin on human fertility. Animal studies have shown effects on sexual maturation, copulation frequency and pregnancy rate (see section 5.3). The clinical relevance of these findings is unknown.

4.7 Effects on ability to drive and use machines

The ability to engage in activities such as operating machinery or operating a motor vehicle may be impaired, especially when initiating therapy. The drug may also induce drowsiness. Patients should not drive or operate machinery unless it has been shown not to affect their alertness or dexterity.

4.8 Undesirable effects

Hypotension: In clinical trials involving patients with hypertension, the most common reactions associated with Doxazosin therapy were of a postural type(rarely associated with fainting) or non-specific.

Benign prostatic hyperplasia: Experience in controlled clinical trials in BPH indicates a similar adverse event profile to that seen in hypertension.

The following undesirable effects have been observed and reported during treatment with Doxazosin with the following frequencies: 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).

System Organ Class	**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)**	**Unknown**
Infections and infestations		Respiratory tract infection, urinary tract infection				
Blood and the lymphatic system disorders					Leukopenia, thrombocytopenia	
Immune system disorders			Allergic drug reaction			
Metabolism and nutrition disorders			Gout, increased appetite, anorexia			
Psychiatric disorders			Agitation, depression, anxiety, insomnia, nervousness			
Nervous system disorders		Somnolence, dizziness, headache	Cerebrovascular accident, hypoesthesia, syncope, tremor		Dizziness postural, paraesthesia	
Eye disorders					Blurred vision	Intraoperative floppy iris syndrome (see section 4.4)
Ear and labyrinth disorders		Vertigo	Tinnitus			
Cardiac disorders		Palpitation, tachycardia	Angina pectoris, myocardial infarction		Bradycardia, cardiac arrhythmias	

Vascular disorders		Hypotension, postural hypotension			Hot flushes	
Respiratory, thoracic and mediastinal disorders		Bronchitis, cough, dyspnoea, rhinitis	Epistaxis		Bronchospasm	
Gastrointestinal disorders		Abdominal pain, dyspepsia, dry mouth, nausea	Constipation, flatulence, vomiting, gastroenteritis, diarrhoea			
Hepato-biliary disorders			Abnormal liver function tests		Cholestasis, hepatitis, jaundice	
Skin and subcutaneous tissue disorders		Pruritus	Skin rash		Urticaria, alopecia, purpura	
Musculoskeletal, connective tissue and bone disorders		Back pain, myalgia	Arthralgia	Muscle cramps, muscle weakness		
Renal and Urinary disorders		Cystitis, Urinary incontin-ence	Dysuria, micturition frequency, haematuria	Polyuria	Increased diuresis, Micturition disorder, nocturia	
Reproductive system and breast disorders			Impotence		Gynecomastia, priapism	Retrograde ejaculation
General disorders and administration site conditions		Asthenia, chest pain, influenza-like symptoms, peripheral oedema	Pain, facial oedema		Fatigue, malaise	
Investigations			Weight increase			

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 Netherlands Pharmacovigilance Centre Lareb, website: www.lareb.nl.

4.9 Overdose

Should overdosage lead to hypotension, the patient should be immediately placed in a supine, head down position. Other supportive measures should be performed if thought appropriate in individual cases.

If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressor should then be used. Renal function should be monitored and supported as needed. Since doxazosin is highly protein bound, dialysis is not indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists
ATC code: C02CA04

Administration of Doxazosin reduces blood pressure due to a decrease in systemic vascular resistance. With once daily dosing, clinically significant reductions in blood pressure are maintained throughout the day and at 24 hours post-dose. During the onset of therapy, a gradual reduction in blood pressure occurs, and orthostatic effects are comparable with those of other antihypertensives.

Doxazosin has been shown to be free of adverse metabolic effects and is suitable for use in patients with co-existent diabetes mellitus, insulin resistance and gout.

Doxazosin is suitable to use in patients with co-existent asthma, left ventricular hypertrophy and in elderly patients.

Treatment with Doxazosin has been shown to result in regression of left ventricular hypertrophy, inhibition of platelet aggregation and enhanced activity of tissue plasminogen activator. Additionally, Doxazosin improves insulin sensitivity in patients who have impairment.

Doxazosin produces favourable effects on blood lipids, with a significant increase in the high density lipoprotein (HDL)/total cholesterol ratio and trends to a favourable reduction in total triglycerides.

Administration of Doxazosin to patients with symptomatic BPH results in a significant improvement in urodynamics and symptoms. The effect in BPH is thought to result from selective blockade of the alpha-adrenoceptors located in the muscular stroma and capsule of the prostate, and in the bladder neck.

Doxazosin has been shown to be an effective blocker of the 1A subtype of the alpha-1-adrenoceptor which accounts for over 70% of the subtypes in the prostate. This accounts for the action in BPH patients.

Doxazosin has demonstrated sustained efficacy and safety in the long-term treatment of BPH.

5.2 Pharmacokinetic properties

Absorption: Following oral administration in humans (young male adults or the elderly of either sex), doxazosin is well absorbed and approximately two thirds of the dose is bioavailable.

Biotransformation/Elimination: Approximately 98% of doxazosin is protein-bound in plasma.

Doxazosin is primarily metabolised by O-demethylation and hydroxylation.

Doxazosin is extensively metabolized in the liver. In vitro studies suggest that the primary pathway for elimination is via CYP 3A4; however, CYP 2D6 and CYP 2C9 metabolic pathways are also involved for elimination, but to a lesser extent.
Doxazosin is extensively metabolised in man and in the animal species tested, with the faeces being the predominant route of excretion.

The mean plasma elimination half-life is 22 hours thus making the drug suitable for once daily administration.

After oral administration of doxazosin the plasma concentrations of the metabolites are low. The most active (6' hydroxy) metabolite is present in man at one fortieth of the plasma concentration of the parent compound which suggests that the antihypertensive activity is in the main due to doxazosin.

Pharmacokinetic studies in the elderly and patients with renal insufficiency have shown no significant alterations compared to younger patients with normal renal function.

There are only limited data in patients with liver impairment and on the effects of drugs known to influence hepatic metabolism (e.g. cimetidine). In a clinical study in 12 subjects with moderate hepatic impairment, single dose administration of doxazosin resulted in an increase in AUC of 43% and a decrease in apparent oral clearance of 40%. As with any drug wholly metabolised by the liver, use of Doxazosin in patients with impaired liver function should be undertaken with caution (see section 4.4).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional animal studies in safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity and gastrointestinal tolerance.

Although no teratogenic effects were seen in animal testing, reduced foetal survival was observed in animals at doses approximately 300 times greater than the maximum human recommended dose.

In repeat-dose toxicity studies in rats, effects on sexual maturation, including delayed vaginal opening and testicular descent, were observed at all tested doses. The reversibility of these findings was not established. In a fertility study in male rats, a reversible reduction in copulation frequency and pregnancy rate was observed at oral doses of 20 mg/kg/day (approximately 4-fold the human AUC at the maximum recommended dose)

Doxazosin transfer into breast milk is minimal, with peak milk levels of 4.2 mcg/L observed 1 hour after a 4 mg dose, and an average concentration of 2.9 mcg/L over 18 hours. A fully breastfed infant would receive about 0.6% of the maternal dose. In a case study, 30 hours after an 8 mg dose, no doxazosin was detected in breast milk, supporting the drug's minimal transfer. Although doxazosin crosses the placenta, fetal drug concentrations remained lower than maternal levels, at least at a dose of 8 mg.

For further information see section 4.6.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl Parahydroxybenzoate (E218)
Propyl Parahydroxybenzoate (E216)
Simethicone Emulsion 30% (contains, benzoic acid (E210), low volatile simethicone intermediate, polyoxyethylene sorbitan tristearate, methylcellulose, poly (ethylene oxide), stearate, glyceryl stearate, xanthan gum, sorbic acid, sulfuric acid 98% & purified water)
Microcrystalline Cellulose and Carmellose Sodium
Glycerol (E422)
Sucralose (E955)
Citric acid anhydrous (E 330)
Lemon flavour (contains propylene glycol (E1520))
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months
Discard 30 days after first opening.

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Container: Type III amber colour glass bottle

Closure: Child resistant, tamper evident plastic (polyethylene/polypropylene) cap with EPE liner

Measuring device: A 20 ml oral syringe with 0.5 ml graduation marks, 10 ml oral syringe with 0.25 ml graduation marks, and a syringe adaptor.

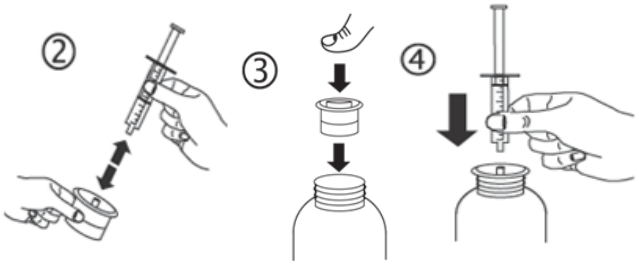
Pack size: 150 ml.

6.6 Special precautions for disposal and other handling

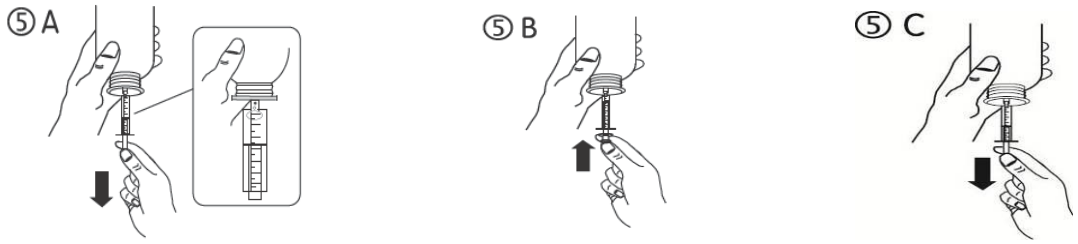
Instructions for the use of syringe:

a) Open the bottle: press the cap and turn it anticlockwise (figure 1).

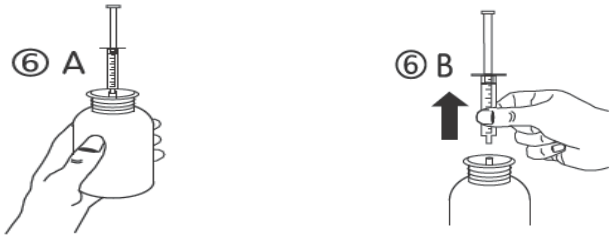
b) Separate the adaptor from the syringe (figure 2). Insert the adaptor into the bottle neck (figure3). Ensure it is properly fixed. Take the syringe and put it in the adaptor opening (figure 4).



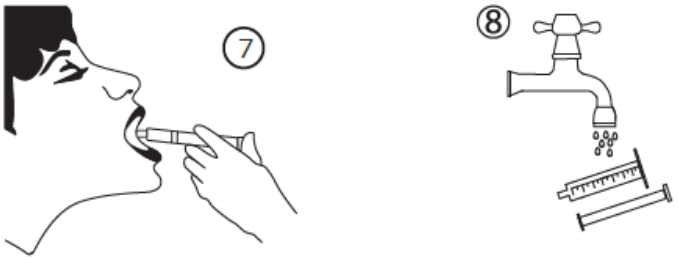
c) Turn the bottle upside down. Fill the syringe with a small amount of suspension by pulling the piston down (figure 5A), then push the piston upwards in order to remove any possible bubble (figure 5B).
Pull the piston down to the graduation mark corresponding to the quantity in millilitres (ml) prescribed by your doctor (figure 5C).



d) Turn the bottle the right way up (figure 6A). Remove the syringe from the adaptor (figure 6B).



e) Empty the contents of the syringe into the patient's mouth by pushing the piston to the bottom of the syringe (figure 7). The contents of the syringe should be emptied into the side cheek of the patient's mouth to avoid a choking hazard. Close the bottle with the plastic cap. Wash the syringe with water (figure 8).



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

7. MARKETING AUTHORISATION HOLDER

Syri Pharma Limited
1 Windmill Lane
Dublin 2, D02 F206
Ierland.

8. MARKETING AUTHORISATION NUMBER(S)

RVG 133857

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 3 november 2025

10. DATE OF REVISION OF THE TEXT