APPROVED PROFESSIONAL INFORMATION FOR PLERINTRA

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

PLERINTRA 25 mg (film-coated tablet)

PLERINTRA 50 mg (film-coated tablet)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PLERINTRA 25 mg

Each film-coated tablets contain 25 mg of Eplerenone.

PLERINTRA 50 mg

Each film-coated tablets contain 50 mg of Eplerenone

Contains sugar “lactose monohydrate”

Each film-coated tablets contains 36,465 mg lactose monohydrate.

Each film-coated tablets contains 72,930mg lactose monohydrate.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

PLERINTRA 25 mg

Light yellow, Round, biconvex, film-coated tablets debossed with "V" on one side and "68" on other side.

PLERINTRA 50 mg

Light yellow, round, biconvex, film-coated tablets debossed with "V' on one side and "67" on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PLERINTRA is indicated to reduce the risk of cardiovascular death in stable patients with left ventricular dysfunction (ejection fraction ≤ 40 %) and clinical evidence of heart failure after an acute myocardial infarction.

4.2 Posology and method of administration

Posology

PLERINTRA is usually administered in combination with Standard therapies. The recommended dose in of **[PRODUCTNAME]** is 50 mg once daily. Treatment should be initiated at 25 mg once daily and titrated to the target dose of 50 mg once daily preferably within 4 weeks as tolerated by the patient taking into account the serum potassium level (see Table 1). After initiation, the dose should be adjusted based on the serum potassium level as shown in Table 1.

Table 1. Dose adjustment table in heart failure – post MI

Serum potassium (mmol/L or mEq/L)	Action	Dose adjustment
< 5,0	Increase	25 mg EOD to 25 mg OD 25 mg OD to 50 mg OD
5,0 – 5,4	5,0 – 5,4	No dose adjustment
5,5 – 5,9	Decrease	50 mg OD to 25 mg OD 25 mg OD to 25 mg EOD 25 mg EOD to withhold
≥ 6,0	Withhold	N/A
EOD (every other day), OD (once daily)		

Following withholding **PLERINTRA** due to serum potassium ≥ 6,0 mmol/L (or > 6,0 mEq/L), **PLERINTRA** can be re-started at a dose of 25 mg every other day when potassium levels have fallen below 5,0 mmol/L (or 5,0 mEq/L).

Special populations

Elderly

No dose adjustment is required in the elderly.

Renal impairment

No initial dose adjustment is required in patients with mild renal impairment (see section 4.4)

Hepatic impairment

No initial dosage adjustment is necessary for patients with mild to moderate hepatic impairment

Paediatric Population

There are insufficient data to recommend the use of **PLERINTRA** in the paediatric population, and therefore, use in this age group is not recommended

Method of Administration

For oral use.

[PRODUCTNAME] may be administered with or without food.

4.3 Contraindications

- Hypersensitivity to eplerenone or to any of the excipients listed in section 6.1
- Patients with serum potassium level > 5.0 mmol/L at initiation
- Patients with severe renal insufficiency (eGFR <30 mL per minute per 1.73 m2)
- Patients with severe hepatic insufficiency (Child-Pugh Class C)
- Patients receiving potassium-sparing diuretics or strong inhibitors of CYP 3A4 (e.g., itraconazole, ketoconazole, ritonavir, nelfinavir, clarithromycin, telithromycin and nefazodone) (see section 4.5)
- The combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) with eplerenone

4.4 Special warnings and precautions for use

Hyperkalaemia

Hyperkalaemia may occur with **PLERINTRA**. Serum potassium levels should be monitored in all patients at initiation of treatment and with a change in dosage. Thereafter periodic monitoring is recommended in patients at risk for the development of hyperkalaemia.

Dose reduction of **PLERINTRA** has been shown to decrease serum potassium level. In one study, the addition of hydrochlorothiazide to **PLERINTRA** therapy has been shown to offset increases in serum potassium. The risk of hyperkalaemia may increase when **PLERINTRA** is used in combination with an angiotensin converting enzyme (ACE) inhibitor and/or an angiotensin receptor blocker (ARB).

Impaired renal function:

Potassium levels should be monitored regularly in patients with impaired renal function, including diabetic microalbuminuria. Patients who have· serum creatinine levels > 221 µmol/L (> 2,5 mg/dL) or creatinine clearance < 50 ml/min should be treated with caution.

While the data from EPHESUS in patients with type 2 diabetes and microalbuminuria is limited, an increased occurrence of hyperkalaemia was observed in this small number of patients. Therefore, these patients should be treated with caution.

Impaired hepatic function:

No elevations of serum potassium above 5,5 mmol/L were observed in patients with mild to moderate hepatic impairment. Electrolyte levels should be monitored in patients with mild to moderate hepatic impairment. The use of **PLERINTRA** in patients with severe hepatic impairment (Child-Pugh Class C) has not been evaluated and therefore contraindicated (see section 4.3).

Non-steroidal anti-inflammatory drugs (NSAIDs):

The administration of other potassium-sparing medicine with NSAIDs has been shown to result in hyperkalaemia in patients with impaired renal function (see section 4.5).

CYP3A4 inducers:

Co-administration of eplerenone with strong CYP3A4 inducers is not Recommended (see section 4.5).

Lithium, cyclosporin, tacrolimus:

Lithium toxicity has been reported in patients receiving lithium concomitantly with diuretics and ACE inhibitors. Serum lithium levels should be monitored frequently if **PLERINTRA** is administered concomitantly with lithium (see section 4.5).

Elderly

Due to age-related decline in renal function, the risk of hyperkalaemia is increased in elderly patients. Periodic monitoring of serum potassium is recommended.

Lactose

The tablets contain lactose and should not be administered in patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption.

Sodium:

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

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Potassium-sparing diuretics and potassium supplements

PLERINTRA should not be administered to patients receiving other potassium-sparing diuretics (see section4.3).

Potassium-sparing diuretics may also potentiate the effect of anti-hypertensive medicine and other

diuretics.

ACE inhibitors, ARBs

The risk of hyperkalaemia may increase when eplerenone is used in combination with an ACE inhibitor and/or an ARB. A close monitoring of serum potassium and renal function is recommended, especially in patients at risk for impaired renal function, e.g., the elderly. The triple combination of an ACE inhibitor and an ARB with eplerenone should not be used (see sections 4.3 and 4.4).

Lithium

Drug interaction studies of **PLERINTRA** have not been conducted with lithium. Lithium toxicity has been reported in patients receiving lithium concomitantly with diuretics and ACE inhibitors (see section 4.4).

Cyclosporin, tacrolimus

Cyclosporin and tacrolimus may lead to impaired renal function and increase the risk of hyperkalaemia. The concomitant use of eplerenone and cyclosporin or tacrolimus should be avoided. If needed, close monitoring of serum potassium and renal function are recommended when cyclosporine and tacrolimus are to be administered during treatment with eplerenone (see section 4.4).

Non-steroidal anti-inflammatory drugs (NSAIDs)

Acute renal failure may occur in at risk patients (elderly, dehydrated subjects, using diuretics, with impaired renal function) due to decreased glomerular filtration (inhibition of vasodilatory prostaglandins due to non-steroidal anti-inflammatory drugs). These effects are generally reversible. Furthermore, there may be a reduction of the antihypertensive effect. Hydrate the patient and monitor renal function at the beginning of treatment and regularly during the combination (see sections 4.2 and 4.4.).

Trimethoprim

The concomitant administration of trimethoprim with eplerenone increases the risk of hyperkalaemia. Monitoring of serum potassium and renal function should be made, particularly in patients with renal impairment and in the elderly.

Alpha1-blockers (e.g. prazosin, alfuzosine)

When alpha1-blockers are combined with eplerenone, there is the potential for increased hypotensive effect and/or postural hypotension. Clinical monitoring for postural hypotension is recommended during alpha1-blocker co-administration.

Tricyclic anti-depressants, neuroleptics, amifostine, baclofen

Co-administration of these medicines with eplerenone may potentially increase antihypertensive effects and risk of postural hypotension.

Glucocorticoids, tetracosactide

Co-administration of these medicines with eplerenone may potentially decrease antihypertensive effects (sodium and fluid retention).

Pharmacokinetic interactions

In vitro studies indicate that eplerenone is not an inhibitor of CYP1A2, CYP2C19, CYP2C9, CYP2D6 or CYP3A4 isozymes. Eplerenone is not a substrate or an inhibitor of P-Glycoprotein.

Digoxin

Systemic exposure (AUC) to digoxin increases by 16% (90% CI: 4 – 30%) when co-administered with eplerenone. Caution is warranted when digoxin is dosed near the upper limit of therapeutic range.

Warfarin

No clinically significant pharmacokinetic interactions have been observed with warfarin. Caution is

warranted when warfarin is dosed near the upper limit of therapeutic range.

CYP3A4 substrates

Results of pharmacokinetic studies with CYP3A4 probe-substrates, i.e. midazolam and cisapride, showed no significant pharmacokinetic interactions when these medicines were co-administered with eplerenone.

CYP3A4 inhibitors

- Strong CYP3A4 inhibitors: Significant pharmacokinetic interactions may occur when eplerenone is co-administered with medicines that inhibit the CYP3A4 enzyme. A strong inhibitor of CYP3A4 (ketoconazole 200 mg BID) led to a 441% increase in AUC of eplerenone (see section 4.3). The concomitant use of eplerenone with strong CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin, telithromycin and nefazadone, is contraindicated (see section 4.3).
- Mild to moderate CYP3A4 inhibitors: Co-administration with erythromycin, saquinavir, amiodarone, diltiazem, verapamil or fluconazole has led to significant pharmacokinetic interactions with rank order increases in AUC ranging from 98% to 187%. Eplerenone dosing should therefore not exceed 25 mg daily when mild to moderate inhibitors of CYP3A4 are co-administered with eplerenone (see section 4.2).

CYP3A4 inducers

Co-administration of *St. John's Wort* (a strong CYP3A4 inducer) with eplerenone caused a 30 % decrease in eplerenone AUC. A more pronounced decrease in eplerenone AUC may occur with stronger CYP3A4 inducers such as rifampicin. Due to the risk of decreased eplerenone efficacy, the concomitant use of strong CYP3A4 inducers (rifampicin, carbamazepine, phenytoin, phenobarbital, *St. John's Wort*) with eplerenone is not recommended (see section 4.4).

Antacids

Based on the results of a pharmacokinetic clinical study, no significant interaction is expected when

antacids are co-administered with eplerenone.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data on use of **PLERINTRA** in pregnant women. Animal studies did not indicate direct or indirect adverse effects with respect to pregnancy, embryofoetal development, parturition and postnatal development. Caution should be exercised prescribing eplerenone to pregnant women.

Breastfeeding:

It is unknown if **PLERINTRA** is excreted in human breast milk after oral administration. however, preclinical data show that eplerenone and/or metabolites are present in rat breast milk and that rat pups exposed by this route developed normally. **PLERINTRA** should not be used during lactation.

Fertility

There are no human data available on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effect of **PLERINTRA** on the ability to drive or use machines have been performed. **PLERINTRA** does not cause drowsiness or impairment of cognitive function but when driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

4.8 Undesirable effects

a) Summary of the safety profiles

PLERINTRA has been evaluated for safety in 3 307 patients treated for heart failure post-myocardial infarction (see section 5.1), In the **PLERINTRA** post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS), the overall incidence of adverse events reported with eplerenone (78,9 %) was similar to placebo (79,5 %). The discontinuation rate due to adverse

events in these studies was 4;4 % for patients receiving eplerenone and for 4,3 % patients receiving placebo. Adverse events reported below are those with suspected relationship to treatment and in excess of placebo, taken from EPHESUS. Adverse events are listed by body system and absolute frequency.

MedDRA system organ class	**Adverse reaction**
Infections and infestations	
Less frequent:	Pyelonephritis, infection, pharyngitis
Blood and lymphatic system disorders	
Less frequent:	Eosinophilia
Endocrine disorders	
Less frequent:	Hypothyroidism
Metabolism and nutrition disorders	
Frequent:	Hyperkalaemia (see sections 4.3 and 4.4), hypercholesterolaemia
Less frequent:	Hyponatraemia, dehydration, hypertriglyceridaemia
Psychiatric disorders	
Frequent:	Insomnia
Nervous system disorders	
Frequent:	Dizziness, syncope, headache
Less frequent:	Hypoaesthesia
Cardiac disorders	
Frequent:	Left ventricular failure, atrial fibrillation
Less frequent:	Tachycardia
Vascular disorders	
Frequent:	Hypotension
Less frequent:	Arterial thrombosis limb, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	

Frequent:	Cough
Gastrointestinal disorders	
Frequent:	Diarrhoea, nausea, constipation, vomiting
Less frequent:	Flatulence
Skin and subcutaneous tissue disorders	
Frequent:	Rash, pruritus
Less frequent:	Hyperhidrosis, angioedema
Musculoskeletal and connective tissue disorders	
Frequent:	Muscle spasms, back pain
Less frequent:	Musculoskeletal pain
Renal and urinary disorders	
Frequent:	Renal impairment (see sections 4.4 and 4.5
Hepatobiliary disorders	
Less frequent:	Cholecystitis
Reproductive system and breast disorders	
Less frequent:	Gynaecomastia
General disorders and administration site conditions	
Frequent:	Asthenia
Less frequent:	Malaise
Investigations	
Frequent:	Blood urea increased, blood creatinine increased
Less frequent:	Epidermal growth factor receptor decreased, blood glucose increased

In EPHESUS, there were numerically more cases of stroke in the very elderly group (≥ 75 years old). There was however no statistically significant difference between the occurrence of stroke in the eplerenone (30) vs. placebo (22) groups. In EMPHASIS-HF, the number of cases of stroke in the very elderly (≥ 75 years old) was 9 in the eplerenone group and 8 in the placebo group.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website 8 or to the Holder of certificate of registration through the mail: pvg.cdma@heterogroups.com.

4.9 Overdose

No cases of human of overdosage with **PLERINTRA** have been reported. The most likely manifestation of human overdosage would be anticipated to be hypotension hyperkalaemia. **PLERINTRA** cannot be removed by haemodialysis. **PLERINTRA** has been shown to bind extensively to charcoal.

If symptomatic hypotension should occur supportive treatment should be initiated. If hyperkalaemia develops, standard treatment should be initiated

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: aldosterone antagonists

ATC code: C03DA04.

CATEGORY AND CLASS

A 6.4 Cardiac medicines- Others

Mechanism of action

Eplerenone has relative selectivity in binding to recombinant human mineralocorticoid receptors compared to its binding to recombinant human glucocorticoid, progesterone and androgen receptors.

Eplerenone prevents the binding of aldosterone, a key hormone in the renin-angiotensin-

aldosterone-system (RAAS), which is involved in the regulation of blood pressure and the pathophysiology of CV disease.

Pharmacodynamic effects

Eplerenone produces sustained increases in plasma renin and serum aldosterone consistent with inhibition of the negative regulatory feedback of aldosterone on renin secretion. Eplerenone was studied in the eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS). EPHESUS was a large multi-center, double-blind, placebo- controlled study in 6 632 patients with acute myocardial infarction (MI), left ventricular dysfunction (as measured by left ventricular ejection fraction [LVEF] < 40 %), and clinical signs of heart failure. Patients were randomised into EPHESUS 3 to 14 days after the index MI, the average time to enrolment was 7 days.

Because of the increased CV risk associated with diabetes, patients with diabetes and LV-dysfunction were eligible for randomisation in the absence of symptoms of HF; 1 D % of the population met this criterion. Patients received eplerenone or placebo in addition to standard therapies at an initial dose 25 mg once daily and titrated to the target dose of 50 mg once daily after 4 weeks if serum potassium was <"5,0 mEq/L. During the study patients received standard care including aspirin (92 %), ACE inhibitors (90 %), β-blockers (83 %), nitrates (72 %), loop diuretics (66 %), or HMG CoA reductase inhibitors (60 °/o). In EPHESUS, eplerenone reduced the risk of death from any cause by 15 % (RR 0,85; 95 % CI, 0,75 - 0,96; p = 0,008). The most common cause of death was cardiovascular death (12,3 %),4,9 % being attributed to sudden death. The risk of cardiovascular (CV) death or CV hospitalisation (cardiovascular hospitalisations were those due to stroke, AMI, ventricular arrhythmias, and heart failure) was reduced by 13 % with eplerenone (RR 0,87; 95% CI, 0,79 - 0,95: p = 0,002). NYHA functional classification improved or remained stable for a significantly greater proportion of patients- receiving eplerenone compared to placebo.

In dose-ranging studies of chronic heart failure (NYHA classification II-IV), the addition of eplerenone to standard therapy resulted in dose-dependent increases in aldosterone. Similarly, in a cardiorenal sub study of EPHESUS, therapy with eplerenone led to a significant increase in

aldosterone. These results confirm the blockade of the mineralocorticoid receptor in these populations.

Paediatric population

Eplerenone has not been studied in paediatric subjects with heart failure. In a 10-week study of paediatric subjects with hypertension (age range 4 to 16 years, n = 304), eplerenone, at doses (from 25 mg up to 100 mg per day) that produced exposure similar to that in adults, did not lower blood pressure effectively. In this study and in a 1-year paediatric safety study in 149 subjects (age range 5 to 17 years), the safety profile was similar to that of adults. Eplerenone has not been studied in hypertensive subjects less than 4 years old because the study in older paediatric subjects showed a lack of efficacy (see section 4.2). Any (long term) effect on hormonal status in paediatric subjects has not been studied

5.2 Pharmacokinetic properties

Absorption

Eplerenone is cleared predominantly by cytochrome P450 (GYP) 3A4 metabolism, with an elimination half-life of 4 to 6 hours. Steady state is reached within 2 days. Absorption is not affected by food. Inhibitors of CYP3A4 (e.g. ketoconazole, saquiriavir) increase blood levels of eplerenone.

Mean peak plasma concentrations of eplerenone are reached approximately 1,5 hours following oral administration. The absolute bioavailability of eplerenone is unknown. Both peak plasma levels (C_{max} and area under the curve (AUC) are dose proportional for doses of 25 to 100 mg and less than proportional at doses above 100 mg.

Distribution

The plasma protein binding of eplerenone is about 50: % and is primarily bound to alpha 1-acid glycoproteins. The apparent volume of distribution at steady state ranged from 43 to 90 L. Eplerenone does not preferentially bind to red blood cells

Biotransformation

Eplerenone metabolism is primarily mediated via CYP3A4. No Active metabolites of eplerenone have been identified in human plasma.

Elimination

Less than 5 % of an eplerenone dose is recovered as unchanged drug in the urine and faeces. Following a single oral dose of radiolabelled drug, approximately 32 % of the dose was excreted in the faeces and approximately 67 % was excreted in the urine. The elimination half-life of eplerenone is approximately 4 to 6 hours. The apparent plasma clearance is approximately 10 L/hr.

Special populations

Age, gender and race:

The pharmacokinetics of eplerenone at a dose of 100 mg-once daily have been Investigated in the elderly (≥ 65 years), in males and females, and in blacks. The pharmacokinetics of eplerenone did not differ significantly between males and females. At steady state, elderly subjects had increases in C_{max} (22 %) and AUC (45 %) compared with younger subjects (18 to 45 years). At steady state, C_{max} was 19 % lower and AUC was 26 % lower in blacks (see section 4.2)

Renal insufficiency.

The pharmacokinetics of eplerenone were evaluated in patients with varying degrees of renal insufficiency and in patients undergoing haemodialysis. Compared with control subjects, steady stale AUC and C_{max} were increased by 38 % and 24 %, respectively, in patients, with severe renal Impairment and a were decreased by 26 % and 3 %, respectively, in patients undergoing haemodialysis. No correlation was observed between plasma clearance of eplerenone and creatinine clearance. Eplerenone is not removed by haemodialysis (see section 4.2)

Hepatic insufficiency:

The pharmacokinetics of eplerenone 400 mg have been investigated in patients with moderate (Child-Pugh Class B) hepatic Impairment and compared with normal subjects steady state C_{max} and AUC of eplerenone were increased by 3,6 % and 42 %, respectively (see section 4.2)

Heart failure:

The pharmacokinetics of eplerenone 50 mg were evaluated in patients with heart failure (NYHA classification II-IV): Compared with healthy subjects matched according to age, weight and gender: steady state AUC and C_{max} in heart failure patients were 38 % and 30 % higher, respectively. Consistent with these results, a population pharmacokinetic analysis of eplerenone based on a subset of patients from EPHESUS indicates that clearance of eplerenone in patients with heart failure was similar to that in healthy elderly subjects

Paediatric population

A population pharmacokinetic model for eplerenone concentrations from two studies in 51 paediatric hypertensive subjects of ages 4 to 16 years identified that patient body weight had a statistically significant effect on eplerenone volume of distribution but not on its clearance. Eplerenone volume of distribution and peak exposure in a heavier paediatric patient are predicted to be similar to that in an adult of similar body weight; in a lighter 45 kg patient, the volume of distribution is about 40% lower and the peak exposure is predicted to be higher than typical adults. Eplerenone treatment was initiated at 25 mg once daily in paediatric patients and increased to 25 mg twice daily after 2 weeks and eventually to 50 mg twice daily, if clinically indicated. At these doses, the highest observed eplerenone concentrations in paediatric subjects were not substantially higher than those in adults initiated at 50 mg once daily.

6. Pharmaceutical particulars

6.1 List of excipients

- The active substance eplerenone
- Lactose Monohydrate
- Micro crystalline cellulose
- Sodium Lauryl Sulphate
- Croscarmellose sodium
- Hypromellose

- Talc
- Magnesium stearate

Composition of Opadry Yellow YS-1-12524-A

- Hypromellose E464
- Titanium dioxide E171
- Macrogol/PEG E1521
- Polysorbate E433
- Iron oxide yellow E172

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light and moisture.

Keep the bottle tightly closed

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

30's and 90's Count HDPE Container HDPE Container 60cc with 33 mm neck (H.W) Child Resistant Plastic Caps with Pulp Liners 33 mm

10's White Opaque PVC-Alu Blister pack

Film White opaque PVC width 200mm 250 µ Plain aluminium foil 25 µ (Hard tempered) 196 mm

10's White Opaque PVC-Peel Push Blister pack

Film White opaque PVC width 200mm 250 µ Plain Peel-Push Through foil (50 GSM Paper/12 µ PET/20 µ Aluminium foil/7 GSM HSL) coating on bright side, width 200 mm

500's bulk pack

Poly bags LDPE DMF Clear (9"x12") 92 GSM, Silica Gel Sachet 5 gram, Plain triple laminated bag (13" x 16") (12 Microns PET/ 12 Microns aluminium foil/110 Microns LDPE)

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER (S)

PLERINTRA 25 mg: 57/6.4/0052

PLERINTRA 50 mg: 57/6.4/0053

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 January 2026

10 DATE OF REVISION OF THE NEXT