SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

Tramadol 100 SR Biotech Sustained-release Tablets

Tramadol 200 SR Biotech Sustained-release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tramadol 100 SR Biotech: each sustained-release tablet contains 100 mg tramadol hydrochloride.

Tramadol 200 SR Biotech: each sustained-release tablet contains 200 mg tramadol hydrochloride.

Tramadol 100 SR Biotech: tablets contain sugar (36 mg lactose monohydrate per tablet).

Tramadol 200 SR Biotech: tablets contain sugar (20 mg lactose monohydrate per tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sustained-release tablets.

Tramadol 100 SR Biotech tablets are white to off white round, biconvex film-coated tablets with “100” embossed on one side and plain on other side.

Tramadol 200 SR Biotech tablets are light orange to light pink, round, biconvex film-coated tablets with “200” embossed on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Management of moderate to severe pain.

4.2 Posology and method of administration

The dosage should be adjusted to the intensity of pain and the sensitivity of the individual patient.

Adults and children over 12 years:

The usual initial dose is 100 mg twice daily, to be taken whole, not divided or chewed, with sufficient liquid, with or without meals, preferably mornings and evenings. If pain relief is not adequate, the dose may be increased to 150 mg or 200 mg twice daily.

A total daily dose of 400 mg Tramadol SR Biotech should not be exceeded.

Dosage intervals can be adjusted to individual requirements but should be at least 8 hours. The lowest analgesically effective dose should generally be selected.

Special populations

Children:

On account of the dosage strength, Tramadol SR Biotech is not recommended for children below the age of 12 years.

Elderly:

A downward adjustment of the dose and/or prolongation of the interval between doses are recommended in the elderly (over 75 years).

Renal Insufficiency/Dialysis:

In patients with renal insufficiency the elimination of tramadol hydrochloride is delayed. In these patients, prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In cases of severe renal insufficiency Tramadol SR Biotech tablets are not recommended.

Patients with hepatic impairment:

In patients with hepatic insufficiency the elimination of tramadol hydrochloride is delayed. In these patients, prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In cases of severe hepatic insufficiency Tramadol SR Biotech tablets are not recommended.

Duration of treatment:

Under no circumstances should Tramadol SR Biotech be given for longer than absolutely necessary. If the nature and severity of the disease requires long-term pain treatment, careful checks should be carried out initially and at regular intervals to assess efficacy and adverse events, and to what extent further treatment with Tramadol SR Biotech is necessary.

Method of administration

For oral use.

4.3 Contraindications

- Known hypersensitivity to tramadol hydrochloride or opioids or to any of the excipients listed in section 6.1.
- In acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic medicines.
- It should not be administered to patients who are receiving monoamine oxidase (MAO) inhibitors or within two weeks of their withdrawal.
- Tramadol SR Biotech should not be given to patients with epilepsy.
- Tramadol SR Biotech must not be used for narcotic withdrawal treatment.
- Tramadol SR Biotech should not be given to patients with respiratory depression, or in the presence of cyanosis and excessive bronchial secretions.
- Tramadol SR Biotech should not be given to patients with increased intracranial pressure or central nervous depression due to head injury or cerebral disease.
- Tramadol SR Biotech should not be used in pregnant and breastfeeding women (see section 4.6).
- All children younger than 12 years of age (see section 4.4).
- Postoperative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy.

4.4 Special warnings and precautions for use

Tramadol SR Biotech should not be used in opioid-dependent patients, patients with head injury, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, increased intracranial pressure (see section 4.3).

In patients sensitive to opiates Tramadol 100 SR Biotech should only be used with caution.

Respiratory depression may develop if the recommended dosages are exceeded, or other centrally depressant medicines are given concomitantly (see section 4.5).

Concomitant use of tramadol and sedating medicines such as benzodiazepines or related substances, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedating medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe tramadol concomitantly with sedating medicines, the lowest effective dose of tramadol such as Tramadol 100 SR Biotech should be used, and the duration of the concomitant treatment should be as short as possible.
The patients should be monitored closely for signs and symptoms of respiratory depression and sedation. It is strongly recommended that patients and their caregivers are informed to be aware of these symptoms (see section 4.5).

Tramadol SR Biotech should not be used in the treatment of minor pain.

Tramadol SR Biotech should be used with caution in patients with impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock (see section 4.2).

Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of Tramadol SR Biotech exceed the recommended upper daily dose limit (400 mg) or in patients taking tricyclic anti-depressants or other tricyclic compounds e.g., promethazine, selective serotonin re-uptake inhibitors, MAO-inhibitors and neuroleptics. The risk of seizures may also be increased in patients with epilepsy; with a history of seizures or in patients with a recognised risk for seizures e.g., drug and alcohol

withdrawal, intracranial infections, head trauma, metabolic disorders and naloxone administration with Tramadol SR Biotech overdose.

Tolerance, psychic and physical dependence may develop, especially after long-term use. Tramadol 100 SR Biotech can reinstate physical dependence in patients that have been previously dependent or chronically using other opioids. In patients with a tendency to drug abuse, a history of drug dependence or who are chronically using opioids, treatment with Tramadol SR Biotech is not recommended.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.
Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance.
The risks of developing tolerance should be explained to the patient.
Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.
Patients should be closely monitored for signs of misuse, abuse, or addiction. The clinical need for analgesic treatment should be reviewed regularly.

When a patient no longer requires therapy with Tramadol SR Biotech, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. Symptoms of withdrawal syndrome similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastro-intestinal symptoms.

Other symptoms that have been seen with tramadol discontinuation include panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual central nervous system (CNS) symptoms (i.e., confusion, delusions, depersonalisation, derealisation, paranoia).

Opioid induced hyperalgesia

Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. OIH may manifest as increased levels of pain, more generalised pain (i.e., less focal), or pain from ordinary (i.e., non-painful) stimuli (allodynia) with no evidence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible.

CYP2D6 metabolism

Tramadol, as contained in Tramadol SR Biotech, is metabolised by the liver enzyme CYP2D6. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect may not be obtained. However, if the patient is an ultra-rapid metaboliser there is a risk of developing side effects of opioid toxicity even at commonly prescribed doses.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal.

Hyponatraemia

Hyponatraemia has been reported with the use of tramadol, usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medications that may cause hyponatraemia. This hyponatraemia appeared to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and resolved with discontinuation of tramadol and appropriate treatment (e.g., fluid restriction). During Tramadol SR Biotech treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic medicines or tramadol alone (see sections 4.5, 4.8 and 4.9).

If concomitant treatment with other serotonergic medicines is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations.

Symptoms of serotonin syndrome may include mental status changes, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms. Serotonin syndrome is likely when one of the following is observed:

Spontaneous clonus: Inducible or ocular clonus with agitation or diaphoresis

Tremor and hyperreflexia: Hypertonia and body temperature > 38 °C and inducible or ocular clonus.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms. Withdrawal of the serotonergic medicines usually brings about a rapid improvement.

Adrenal insufficiency

Opioid analgesics may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g., severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss.

Paediatric population

Tramadol SR Biotech is not suitable for children under 12 years of age.

Post-operative use in children

There have been reports in the published literature that tramadol as contained in Tramadol SR Biotech given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events. Tramadol SR Biotech should not be administered to children younger than 18 years of age following tonsillectomy and/or adenoidectomy (see section 4.3).

Children with compromised respiratory function

Tramadol SR Biotech is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of opioid toxicity.

Tramadol SR Biotech contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take Tramadol SR Biotech.

4.5 Interaction with other medicines and other forms of interaction

Tramadol SR Biotech should not be combined with MAO inhibitors within 14 days of withdrawal of MAO inhibitors (see section 4.3).

In patients treated with MAO inhibitors in the 14 days prior to the use of the opioid pethidine, life-threatening interactions on the central nervous system, respiratory and cardiovascular function have been observed. The same interactions with MAO inhibitors cannot be ruled out during treatment with Tramadol SR Biotech.

Concomitant administration of Tramadol SR Biotech with other centrally depressant medicines including alcohol may potentiate the central nervous system effects (see section 4.3).
The concomitant use of opioids with sedating medicines such as benzodiazepines or related substances increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose of tramadol and the duration of the concomitant use should be limited (see section 4.4).

The results of pharmacokinetic studies have so far shown that on the concomitant or previous administration of cimetidine (enzyme inhibitor) clinically relevant interactions are unlikely to occur. Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action.

Tramadol SR Biotech can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold-lowering medicine (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of Tramadol SR Biotech and serotonergic medicines, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonin toxicity.

Serotonin syndrome is likely when one of the following is observed:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature > 38 ˚C and inducible ocular clonus.

Withdrawal of the serotonergic medicines usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

Caution should be exercised during concomitant treatment with Tramadol SR Biotech and warfarin-like medicines due to reports of increased INR with major bleeding and ecchymoses in some patients.

Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied (see section 4.8).

The antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain. Tramadol SR Biotech may decrease the antiemetic efficacy of ondansetron.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/ Contraception in males and females

Patients of child-bearing potential should be advised to use effective contraception while on treatment.

Pregnancy

Safety during pregnancy and lactation has not been established, therefore Tramadol SR Biotech tablets should not be used in pregnant women. Tramadol crosses the placenta. Animal studies with tramadol revealed effects on organ development, ossification and neonatal mortality.

The repeated administration of Tramadol SR Biotech tablets during pregnancy may lead to habituation in the unborn child. The child may experience withdrawal symptoms after birth (see section 4.3).

Breastfeeding

Tramadol as contained in Tramadol SR Biotech passes into breastmilk. Mothers on Tramadol SR Biotech tablets should not breastfeed their infants.

Fertility

Post marketing surveillance does not suggest an effect of tramadol on fertility. Animal studies did not show an effect of tramadol on fertility.

4.7 Effects on ability to drive and use machines

Tramadol SR Biotech may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This applies particularly in conjunction with other psychotropic substances, particularly alcohol.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently reported adverse reaction during treatment with tramadol are nausea and dizziness.

b. Tabulated summary of adverse reactions

System organ class	**Frequency**
Immune system disorders	*Less frequent* Allergic reactions (e.g., dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis
Metabolism and nutrition disorders	*Less frequent* Changes in appetite
	Frequency unknown Hypoglycaemia, hyponatraemia, Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Psychiatric disorders	*Less frequent* Hallucinations, confusion, sleep disturbance, delirium, anxiety and nightmares. Psychic adverse reactions may occur following administration of Tramadol SR Biotech which vary individually in intensity and nature (depending on personality and duration of

	treatment). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial capacity (e.g., decision behaviour, perception disorders).
	Frequency unknown Drug dependence may occur.
Nervous system disorders	*Frequent* Dizziness, headache, somnolence
	Less frequent Speech disorders, paraesthesia, tremor, epileptiform convulsions*, involuntary muscle contractions, abnormal coordination, syncope
	Frequency unknown Serotonin syndrome
Eye disorders	*Less frequent* Miosis, mydriasis, blurred vision
Cardiac disorders	*Less frequent* Dysrhythmias, palpitation, tachycardia, bradycardia
Vascular disorders	*Less frequent* Postural hypotension, cardiovascular collapse, increase in blood pressure
Respiratory, thoracic and mediastinal disorders	*Less frequent* Dyspnoea, respiratory depression, bronchospasm

	Frequency unknown Hiccups, worsening of asthma
Gastrointestinal disorders	*Frequent* Nausea, constipation, dry mouth, vomiting
	Less frequent Retching; gastrointestinal discomfort (a feeling of pressure in the stomach, bloating), diarrhoea
Hepato-biliary disorders	*Less frequent* Increase in transaminases (ALT and AST) is expected
Skin and subcutaneous tissue disorders	*Frequent* Hyperhidrosis
	Less frequent Dermal reactions (e.g., pruritus, rash, urticaria)
	Frequency unknown Stevens Johnson Syndrome, toxic epidermal necrolysis
Musculoskeletal, connective tissue and bone disorders	*Less frequent* Muscular weakness
Renal and urinary disorders	*Less frequent* Micturition disorders (dysuria and urinary retention)
General disorders and administration site conditions	*Frequent* Fatigue
	Less frequent

	Drug withdrawal syndrome

* Convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicines which can lower the seizure threshold (see sections 4.4 and 4.5).

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

Following an overdose with Tramadol SR Biotech, symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular constriction of the pupil of the eye, vomiting, cardiovascular collapse, consciousness disorders, coma, convulsions, respiratory depression and respiratory arrest.

Treatment

The general emergency measures apply. Keep open the respiratory tract, prevent aspiration, maintain respiration and circulation depending on the symptoms. Suitable measures should be taken to avoid aspiration dangers.

Respiratory depression can be antagonised with a pure opiate antagonist (naloxone).

Convulsions should be treated with intravenous diazepam.

In cases of overdosage with oral formulations, gastrointestinal-decontamination with activated charcoal is only recommended within 2 hours after Tramadol SR Biotech intake. Gastrointestinal decontamination at a later time point may be useful in case of overdosage with exceptionally large quantities.

Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore, treatment of acute intoxication with Tramadol SR Biotech with haemodialysis or haemofiltration alone is not suitable for detoxification.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.2.9 Other analgesics

Pharmacotherapeutic group: other opioids; ATC code: N02 AX02

Mechanism of action

Tramadol is a centrally acting opioid analgesic. It is a non-selective pure agonist at μ, δ and κ opioid receptors with a higher affinity for the μ receptor. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.

Tramadol has an antitussive effect. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also, gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

Paediatric population

Effects of enteral and parenteral administration of tramadol have been investigated in clinical trials involving paediatric patients ranging in age from neonate to 17 years of age. The indications for pain treatment studied in those trials included pain after surgery (mainly abdominal), after surgical tooth extractions, due to fractures, burns and traumas as well as other painful conditions likely to require analgesic treatment for at least 7 days.

At single doses of up to 2 mg/kg or multiple doses of up to 8 mg/kg per day (to a maximum of 400 mg per day) efficacy of tramadol was confirmed. However, use of tramadol in children under 12 years is contraindicated (see section 4.2 and 4.3).

5.2 Pharmacokinetic properties

Absorption:

More than 90 % of Tramadol SR Biotech is absorbed after oral administration. The mean absolute bioavailability is approximately 70 %, irrespective of the concomitant intake of food. The difference between absorbed and non-metabolised available tramadol is probably due to the low first-pass effect. The first-pass effect after oral administration is a maximum of 30 %.

Distribution:

Tramadol has a high tissue affinity ($V_{d,ß}$ = 203 + 40 l). It has a plasma protein binding of about 20 %.

After administration of 100 mg of tramadol the peak plasma concentration C_{max} =141 + 40 ng/ml is reached after 4,9 h. After administration of 200 mg tramadol C_{max} 260 + 62 ng/ml is reached after 4,8 hours.

Tramadol hydrochloride crosses the blood-brain and placental barrier. Small amounts are excreted in breast milk unchanged or as the metabolite M1.

Elimination half-life $t_{1/2,\beta}$ is approximately 6 h, irrespective of the mode of administration. In patients above 75 years of age it may be prolonged by a factor of approximately 1,4.

Biotransformation:

In humans, tramadol is mainly metabolised by means of N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. There are considerable interindividual quantitative differences between the other metabolites. So far, eleven metabolites have been found in the urine. Animal experiments have shown that O-desmethyltramadol is more potent than the parent substance by the factor 2 - 4. Its half-life $t_{1/2,\beta}$ is 7,9 h (range 5,4 – 9,6 h) and is approximately that of tramadol.

The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite.

Elimination:

Tramadol hydrochloride and its metabolites are almost completely excreted by the renal route (95 %). Biliary excretion of these components is quantitatively insignificant and is therefore subject to hepatic metabolism and renal elimination. The terminal half-life ($t_{1/2\,\beta}$) is prolonged in impaired hepatic or renal function. In patients with cirrhosis of the liver, elimination half-lives of 13,3 + 4,9 h (tramadol) and 18,5 + 9,4 h (O-desmethyltramadol), in an extreme case 22,3 h and 36 h respectively, have been determined. In patients with renal insufficiency (creatinine clearance < 5 mL/min) the values were 11 + 3,2 h and 16,9 + 3 h, in an extreme case 19,5 h and 43,2 h respectively.

Linearity/non-linearity:

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range.

The relationship between serum concentrations and the analgesic effect is dose-dependent but varies considerably in isolated cases. A serum concentration of 100 - 300 ng/ml is usually effective.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Colloidal anhydrous silica

Hypromellose

Isopropyl Alcohol

Lactose monohydrate

Magnesium stearate

Microcrystalline Cellulose

Tablet coating

Hypromellose

Macrogol 6 000

Talc

Titanium dioxide E171

Additionally for the [TRAMADOL 200 SR BIOTECH]:

Colour Quinoline Yellow E104

Ferric Oxide Red E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a cool, dry place. Store at or below 25 °C.

Keep in the blisters until required for use.

6.5 Nature and contents of container

TRAMADOL SR BIOTECH tablets are packed in white opaque PVC (250 μ) / Aluminium (0,025 mm) blisters of 10 tablets. The blisters are then packaged in an outer carton containing 30 or 60 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Block K West

Central Park

400 16th Road

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1685

South Africa

8. REGISTRATION NUMBER(S)

Tramadol 100 SR Biotech - 56/2.9/0248

Tramadol 200 SR Biotech - 56/2.9/0249

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 October 2023

10. DATE OF REVISION OF THE TEXT

17 October 2023