

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oxycodone Lannacher SR 20 mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film-coated tablet contains 20 mg oxycodone hydrochloride corresponding to 17.93 mg oxycodone.

Excipient with known effect:

Soya lecithin..... 0.105 mg per tablet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Pale pink, round and biconvex film-coated tablets

Diameter: 5.1 mm

Thickness: 3.8 mm

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Severe pain, which requires opioid analgesics to be adequately managed.

4.2 Posology and method of administration

DOSAGE

The dosage depends on the pain intensity and the patient's individual susceptibility to the treatment.

For doses not realisable/practicable with this strength, other strengths of this medicinal product are available.

The following general dosage recommendations apply:

Paediatric population

Oxycodone Lannacher SR is not recommended for children under 12 years of age.

Adults and adolescents 12 years and older

Dose titration and adjustment

In general, the initial dose for opioid-naïve patients is 10 mg oxycodone hydrochloride given at intervals of 12 hours. Some patients may benefit from a starting dose of 5 mg to minimize the incidence of adverse reactions.

Patients already receiving opioids may start treatment with higher dosages taking into account their experience with former opioid therapies.

According to well-controlled clinical studies 10-13 mg oxycodone hydrochloride correspond to approximately 20 mg morphine sulphate, both in the prolonged-release formulation.

Because of individual differences in sensitivity for different opioids, it is recommended that patients should start conservatively with Oxycodone hydrochloride prolonged-release tablets after conversion from other opioids, with 50-75% of the calculated oxycodone dose.

Some patients who take Oxycodone hydrochloride prolonged-release tablets following a fixed schedule need rapid-release analgesics as rescue medication in order to control breakthrough pain. Oxycodone hydrochloride prolonged-release tablets are not indicated for the treatment of acute pain and/or breakthrough pain. The single dose of the rescue medication should

amount to 1/6 of the equianalgesic daily dose of Oxycodone hydrochloride prolonged-release tablets. Use of the rescue medication more than twice daily indicates that the dose of Oxycodone hydrochloride prolonged-release tablets needs to be increased. The dose should not be adjusted more often than once every 1-2 days until a stable twice daily administration has been achieved.

Following a dose increase from 10 mg to 20 mg, taken every 12 hours, dose adjustments should be made in steps of approximately one third of the daily dose. The aim is a patient-specific dosage which, with twice daily administration, allows for adequate analgesia with tolerable undesirable effects and as little rescue medication as possible as long as pain therapy is needed.

Even distribution (the same dose in the morning and in the evening) following a fixed schedule (every 12 hours) is appropriate for the majority of the patients. For some patients it may be advantageous to distribute the doses unevenly. In general, the lowest effective analgesic dose should be chosen. For the treatment of non malignant pain a daily dose of 40 mg is generally sufficient; but higher dosages may be necessary. Patients with cancer-related pain may require dosages of 80 to 120 mg, which in individual cases can be increased to up to 400 mg. If even higher doses are required, the dose should be decided individually balancing efficacy against tolerance and the risk of undesirable effects.

Elderly patients

Elderly patients without clinical manifestation of impaired liver and/or kidney function usually do not require dose adjustments.

Patients with renal or hepatic impairment

The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to his/her clinical situation.

METHOD OF ADMINISTRATION

Oral use.

Oxycodone Lannacher SR prolonged-release tablets should be taken twice daily based on a fixed schedule at the dosage determined.

The prolonged-release tablets may be taken with or independent of meals with a sufficient amount of liquid. Oxycodone Lannacher SR prolonged-release tablets must be swallowed whole, and they must not be chewed, divided or crushed.

DURATION OF ADMINISTRATION

Oxycodone Lannacher SR prolonged-release tablets should not be taken longer than necessary. If long-term treatment is necessary due to the type and severity of the illness, careful and regular monitoring is required to determine whether and to what extent treatment should be continued. If opioid therapy is no longer indicated it may be advisable to reduce the daily dose gradually in order to prevent symptoms of a withdrawal syndrome.

DISCONTINUATION OF TREATMENT

When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent withdrawal symptoms.

4.3 Contraindications

- hypersensitivity to oxycodone hydrochloride, soya, peanut, or to any of the excipients listed in section 6.1
- Oxycodone must not be used in any situation where opioids are contraindicated:
- severe respiratory depression with hypoxia and/or hypercapnia
- elevated carbon dioxide levels in the blood
- severe chronic obstructive pulmonary disease
- cor pulmonale
- severe bronchial asthma
- paralytic ileus
- acute abdomen, delayed gastric emptying

4.4 Special warnings and precautions for use

Caution should be exercised in

- elderly or debilitated patients,
- patients with severe impairment of lung, liver or kidney function,
- myxoedema, hypothyroidism,
- Addison's disease (adrenal insufficiency),
- intoxication psychosis (e.g. alcohol),
- prostatic hypertrophy,
- alcoholism, known opioid dependence,
- delirium tremens,
- pancreatitis,
- diseases of the biliary tract, biliary or ureteric colic,
- conditions with increased brain pressure,
- disturbances of circulatory regulation,
- epilepsy or seizure tendency and
- patients taking MAO inhibitors.

Opioids, such as oxycodone hydrochloride, may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

Respiratory depression

The major risk of opioid excess is respiratory depression. Caution must be exercised when administering oxycodone to the debilitated elderly; patients with severely impaired pulmonary function, impaired hepatic or renal function; patients with myxoedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, adrenocortical insufficiency, alcoholism, delirium tremens, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, hypotension, hypovolaemia, head injury (due to risk of increased intracranial pressure) or patients taking MAO inhibitors.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs

Concomitant use of Oxycodone Lannacher SR and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Oxycodone Lannacher SR concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation.

In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Tolerance and dependence

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control.

Oxycodone Lannacher SR prolonged-release tablets have a primary dependence potential. However, when used as intended in patients with chronic pain the risk of developing physical or psychological dependence is markedly reduced. There are no data available on the actual incidence of psychological dependence in chronic pain patients.

Prolonged use of Oxycodone Lannacher SR prolonged-release tablets may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent withdrawal symptoms.

Withdrawal symptoms may include yawning, mydriasis, lacrimation, rhinorrhoea, tremor, hyperhidrosis, anxiety, agitation, convulsions and insomnia.

Hyperalgesia that will not respond to a further dose increase of oxycodone may very rarely occur, particularly in high doses. An oxycodone dose reduction or change to an alternative opioid may be required.

Abuse

Oxycodone has an abuse profile similar to other strong opioid agonists. Oxycodone may be sought and abused by people with latent or manifest addictive disorders. There is potential for the development of psychological dependence [addiction] to opioid analgesics, including oxycodone. Oxycodone Lannacher SR should be used with particular care in patients with a history of alcohol and drug abuse.

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

The prolonged-release tablets must be swallowed whole, and not broken, crushed or chewed. The administration of broken, chewed or crushed prolonged-release oxycodone tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone (see section 4.9).

Surgical procedures

As with all opioid preparations, oxycodone products should be used with caution following abdominal surgery as opioids are known to impair intestinal motility and should not be used until the physician is assured of normal bowel function. The use of oxycodone prolonged-release tablets is not recommended prior to and during the first 12-24 hours after surgical procedures. If further treatment with oxycodone is indicated, the dose should be adjusted to the new post-operative requirements.

Special care should be taken when oxycodone is used in patients undergoing bowel-surgery. Opioids should only be administered post-operatively when the bowel function has been restored.

The safety of Oxycodone Lannacher SR prolonged-release tablets used pre-operatively has not been established and can therefore not be recommended.

Children

Oxycodone hydrochloride prolonged-release tablets have not been studied in children younger than 12 years of age. The safety and efficacy of the tablets have not been demonstrated and the use in children younger than 12 years of age is therefore not recommended.

Patients with severe hepatic impairment

Patients with severe hepatic impairment should be closely monitored.

Alcohol

Concomitant use of alcohol and Oxycodone Lannacher SR prolonged-release tablets may increase the undesirable effects of Oxycodone Lannacher SR; concomitant use should be avoided.

Anti-Doping Warning

The use of Oxycodone Lannacher SR may produce positive results in doping controls.

Use of Oxycodone Lannacher SR as a doping agent may become a health hazard.

4.5 Interaction with other medicinal products and other forms of interactions

Alcohol may enhance the pharmacodynamic effects of Oxycodone Lannacher SR prolonged-release tablets; concomitant use should be avoided.

Central nervous system depressants (e.g. sedatives, hypnotics, antipsychotics, anaesthetics, antidepressants, muscle relaxants, antihistamines, antiemetics) and other opioids can enhance the CNS depressant effect of oxycodone, in particular respiratory depression.

Concomitant administration of oxycodone with **serotonin agents**, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) may cause serotonin toxicity. The symptoms of serotonin toxicity may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal

symptoms (e.g., nausea, vomiting, diarrhoea). Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

Sedative medicines such as benzodiazepines or related drugs

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Anticholinergics (e.g. antipsychotics, antihistamines, antiemetics, antiparkinson medicines) can enhance the anticholinergic undesirable effects of oxycodone (such as constipation, dry mouth or micturition disorders).

Cimetidine can inhibit the metabolism of oxycodone.

Monoaminoxidase (MAO) inhibitors are known to interact with opioid analgesics, producing CNS excitation or depression with hyper- or hypotensive crisis (see section 4.4). Oxycodone should be used with caution in patients administered MAO-inhibitors or who have received MAO-inhibitors during the last two weeks (see section 4.4).

Clinically relevant changes in International Normalized Ratio (INR) in both directions have been observed in individuals if **coumarin anticoagulants** are co-applied with Oxycodone Lannacher SR prolonged-release tablets.

Oxycodone is metabolised mainly by **CYP3A4**, with a contribution from **CYP2D6**. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azole-type antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may reduce the clearance of oxycodone which could result in an increase of oxycodone plasma concentrations. Therefore the oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered as 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).
- Voriconazole, a CYP3A4 inhibitor, administered as 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).
- Telithromycin, a CYP3A4 inhibitor, administered as 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).
- Grapefruit juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).
- CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin and St John's Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone which could result in a reduction of oxycodone plasma concentrations. The oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- St John's Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).
- Rifampicin, a CYP3A4 inducer, administered as 600 mg once daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower.

Drugs that inhibit CYP2D6 activity, such as paroxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

4.6 Fertility, pregnancy and lactation

Use of this medicinal product should be avoided to the extent possible in patients who are pregnant or lactating.

Pregnancy

There are limited data from the use of oxycodone in pregnant women. Infants born to mothers who have received opioids during the last 3 to 4 weeks before giving birth should be monitored for respiratory depression. Withdrawal symptoms may be observed in the newborns of mothers undergoing treatment with oxycodone.

Breast-feeding

Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxycodone should, therefore, not be used in breastfeeding mothers.

4.7 Effects on ability to drive and use machines

Oxycodone may impair the ability to drive and use machines.

With stable therapy, a general ban on driving a vehicle is not necessary. The treating physician must assess the individual situation.

4.8 Undesirable effects

Oxycodone can cause respiratory depression, miosis, bronchial spasms and spasms of the smooth muscles and can suppress the cough reflex.

The adverse reactions considered at least possibly related to treatment are listed below by system organ class and absolute frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

Frequency unknown cannot be estimated from the available data

Immune system disorders:

Uncommon: hypersensitivity

Frequency unknown: anaphylactic responses

Blood and lymphatic system disorders

Rare: lymphadenopathy

Endocrine disorders

Uncommon: syndrome of inappropriate antidiuretic hormone secretion

Metabolism and nutrition disorders

Common: decreased appetite

Uncommon: dehydration

Psychiatric disorders

Common: anxiety, confusional state, depression, insomnia, nervousness, abnormal thinking Uncommon: agitation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4)

Frequency unknown: aggression

Nervous system disorders

Very common: somnolence, dizziness, headache

Common: tremor

Uncommon: amnesia, convulsion, hypertonia, hypoaesthesia, involuntary muscle contractions, speech disorders, syncope, paraesthesia, dysgeusia

Rare: seizures, particularly in epileptic patients or patients with tendency to convulsions, muscle spasm

Frequency unknown: hyperalgesia

Eye disorders

Uncommon: visual impairment, miosis

Ear and labyrinth disorders

Uncommon: vertigo

Cardiac disorders

Common: lowering of blood pressure, rarely accompanied by secondary symptoms such as palpitations, syncope, bronchospasm

Uncommon: palpitation (in the context of withdrawal syndrome), supraventricular tachycardia

Vascular disorders

Uncommon: vasodilatation

Rare: hypotension, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea

Uncommon: respiratory depression, increased coughing, pharyngitis, rhinitis, voice changes

Gastrointestinal disorders

Very common: constipation, nausea, vomiting

Common: dry mouth, rarely accompanied by thirst and difficulty swallowing; abdominal pain, diarrhoea, dyspepsia

Uncommon: dysphagia, oral ulcers, gingivitis, stomatitis, flatulence, eructation, ileus

Rare: gingival bleeding, increased appetite, tarry stool,

Frequency unknown: dental caries

Hepatobiliary disorders

Uncommon: increase hepatic enzymes

Frequency unknown: cholestasis, biliary colic

Skin and subcutaneous tissue disorders

Very common: pruritus

Common: rash, hyperhidrosis

Uncommon: dry skin

Rare: urticaria, manifestations of herpes simplex, increased photosensitivity

Very rare: exfoliative dermatitis

Renal and urinary disorders

Uncommon: micturition disturbances (urinary retention, but also increased urge to urinate)

Rare: haematuria

Reproductive system and breast disorders

Uncommon: reduced libido, erectile dysfunction

Frequency unknown: amenorrhoea

General disorders and administration site conditions

Common: sweating, asthenic conditions

Uncommon: chills, malaise, accidental injuries, pain (e.g. chest pain), oedema, peripheral oedema, migraine, physical dependence with withdrawal symptoms, drug tolerance, thirst

Rare: weight changes (increase or decrease), cellulitis

Not known: drugwithdrawal syndrome neonatal

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:

HPRA Pharmacovigilance

Website: www.hpra.ie

4.9 Overdose

Symptoms

Acute overdose with oxycodone can be manifested by miosis, respiratory depression, somnolence progressing to stupor or coma, hypotonia, drop in blood pressure and death. In severe cases circulatory collapse, bradycardia and non-cardiogenic lung oedema may occur; abuse of high doses of strong opioids such as oxycodone can be fatal.

Therapy

Primary attention must be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

Pure opioid antagonist such as naloxone (0.4-2 mg intravenous) serve as specific antidotes in the treatment of opioid overdose. Administration of single doses must be repeated depending on the clinical situation at intervals of 2 to 3 minutes. Intravenous infusion of 2 mg of naloxone in 500 ml isotonic saline or 5% dextrose solution (corresponding to 0.004 mg naloxone/ml) is possible. The rate of infusion should be adjusted to the previous bolus injections and the response of the patient.

Gastric lavage can be taken into consideration. The administration of activated charcoal (50 g for adults, 10 -15 g for children) should be considered within 1 hour, if a substantial amount has been ingested within 1 hour, provided the airway can be protected. It may be reasonable to assume that late administration of activated charcoal may be beneficial for prolonged-release preparations; however there is no evidence to support this.

For speeding up the passage a suitable laxative (e.g. a PEG-based solution) may be useful.

Supportive measures (artificial respiration, oxygen supply, administration of vasopressors and infusion therapy) should, if necessary, be applied in the treatment of accompanying circulatory shock. Upon cardiac arrest or cardiac arrhythmias, cardiac massage or defibrillation may be indicated. If necessary, assisted ventilation as well as maintenance of water and electrolyte balance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC code: N02AA05

Oxycodone shows an affinity to kappa, mu and delta opioid receptors in the brain and spinal cord. It acts at these receptors as an opioid agonist without an antagonistic effect. The therapeutic effect is mainly analgesic and sedative. Compared to rapid-release oxycodone, given alone or in combination with other substances, the prolonged-release tablets provide pain relief for a markedly longer period without increased occurrence of undesirable effects.

5.2 Pharmacokinetic properties

Absorption

The relative bioavailability of Oxycodone Lannacher prolonged-release tablets is comparable to that of rapid-release oxycodone with maximum plasma concentrations being achieved after approximately 3 hours after intake of the prolonged-release tablets compared to 1 to 1.5 hours. Peak plasma concentrations and oscillations of the concentrations of oxycodone from the prolonged-release and rapid-release formulations are comparable when given at the same daily dose at intervals of 12 and 6 hours respectively.

The tablets must not be crushed, divided, or chewed as this leads to rapid oxycodone release and absorption of a potentially fatal dose of oxycodone due to the damage of the prolonged-release properties.

Distribution

The absolute oral bioavailability of oxycodone is approximately two thirds relative to parenteral administration. In steady state, the volume of distribution of oxycodone amounts to 2.6 l/kg; plasma protein binding to 38-45%; the elimination half-life to 4 to 6 hours and plasma clearance to 0.8 l/min. The elimination half-life of oxycodone from prolonged-release tablets is 4-5 hours with steady state values being achieved after a mean of 1 day.

Biotransformation

Oxycodone is metabolised in the intestine and liver via the cytochrome P450 system to noroxycodone and oxymorphone as well as to several glucuronide conjugates. In vitro studies suggest that therapeutic doses of cimetidine probably have no relevant effect on the formation of noroxycodone. In man, quinidine reduces the production of oxymorphone while the pharmacodynamic properties of oxycodone remain largely unaffected. The contribution of the metabolites to the overall pharmacodynamic effect is irrelevant.

Elimination

Oxycodone and its metabolites are excreted via urine and faeces. Oxycodone crosses the placenta and is found in breast milk.

Linearity/non-linearity

The 5, 10 and 20 mg prolonged-release tablets are dose-proportional with regard to the amount of active substance absorbed as well as comparable with regard to the rate of absorption.

5.3 Preclinical safety data

There is insufficient data on the reproduction toxicity properties of oxycodone and there is no data available on fertility and postnatal effects following intrauterine exposure. Oxycodone did not cause malformations in rats and rabbits at dosages which were 1.5 to 2.5 times the human dose of 160 mg/day, based on mg/kg basis.

Long-term studies on carcinogenicity have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Kollidon SR (consisting of poly(vinylacetate), povidone (K = 27.0 - 32.4), sodium lauryl sulphate, silica)

Cellulose, microcrystalline

Colloidal anhydrous silica

Magnesium stearate, vegetable

Tablet coating

Polyvinyl alcohol

Talc (E 553b)

Titanium dioxide (E 171)

Macrogol 3350

Lecithin (soya) (E 322)

Iron oxide yellow (E 172)

Iron oxide black (E 172)

Iron oxide red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

PVC/PVdC/aluminium blisters containing 7, 10, 14, 20, 28, 30, 50, 56, 60, 72, 98, and 100 prolonged-release tablets.

Unit-dose blisters of 30x1, 50x1, 56x1, 60x1, 72x1, 98x1, and 100x1 prolonged-release tablets.

Not all pack sizes will be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Lannacher Heilmittel Ges.m.b.H

Schlossplatz 1

8502 Lannach

Austria

8 MARKETING AUTHORISATION NUMBER

PA0947/003/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th September 2010

Date of last renewal: 31st March 2013

10 DATE OF REVISION OF THE TEXT

September 2020