Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tradol 50mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 50 mg tramadol hydrochloride.
One 1ml ampoule contains 50 mg tramadol hydrochloride and one 2 ml ampoule contains 100 mg tramadol hydrochloride
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection or Infusion (short term: injection)
Clear, colourless solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate to severe pain.

4.2 Posology and method of administration

The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected. Daily doses of 400mg of active substance should not be exceeded, unless there are special medical circumstances (e.g. tumour pain and severe pain after surgery).

Treatment goals and discontinuation
Before initiating treatment with Tradol, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Unless otherwise prescribed, Tradol should be administered as follows:

Adults and children above the age of 12 years:
The usual dosage is 50 or 100 mg 4-6 hourly. Intravenous injections must be given slowly over 2-3 minutes. For post-operative pain, administer an initial bolus of 100mg. During the 60 minutes following the initial bolus, further doses of 50 mg may be given every 10-20 minutes, up to a total dose of 250 mg including the initial bolus. Subsequent doses should be 50-100 mg 4-6 hourly up to a total daily dose of 400mg.

Children above the age of 1 year:
The recommended single dose of tramadol hydrochloride is 1 mg/kg to 2 mg/kg body weight. The total daily dose of 8 mg tramadol hydrochloride per kg body weight or 400 mg tramadol hydrochloride, whichever is lower, should not be exceeded per day. On account of their high dosage strengths, capsules, prolonged release tablets and dispersible tablets are not intended for children below the age of 12 years.

Elderly *patients*
A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In elderly patients over 75 years elimination may be prolonged. Therefore, if necessary, the dosage interval is to be extended according to the patient's requirements.

Patients with renal insufficiency/dialysis and hepatic impairment:

In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. In these patients prolongation of dosage intervals should be carefully considered according to the patient's requirements.

Method of administration
The solution for injection is to be injected slowly or diluted in infusion solution and infused.
It can be administered by intramuscular, intravenous, subcutaneous injection or intravenous infusion.

For instructions on dilution of the medicinal product before administration, see section 6.6.

Duration of administration
Tramadol should under no circumstances be administered for longer than absolutely necessary. If long term pain treatment with tramadol is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if necessary) with breaks in the treatment) to establish whether and to what extent further treatment is necessary.

4.3 Contraindications

Tradol is contraindicated
• in hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
• In acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic medicinal products.
• In patients who are receiving monoamine oxidase inhibitors or who have taken them within the last 14 days (*see section 4.5*).
• in patients with epilepsy not adequately controlled by treatment.
• for use in narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

Tramadol may only be used with particular caution 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.

In patients sensitive to opiates the product should only be used with caution.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered (*see section 4.5*), or if the recommended dosage is significantly exceeded (*see section 4.9*), as the possibility of respiratory depression cannot be excluded in these situations.

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnea (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.

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.

Serotonin syndrome
Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone (see sections 4.5, 4.8 and 4.9).
If concomitant treatment with other serotonergic agents 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.
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 drugs usually brings about a rapid improvement.

Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended upper daily dose limit (400mg). In addition, tramadol may increase the seizure risk in patients taking other medicinal products that lowers the seizure threshold (*see section 4.5*).

Patients with epilepsy or those susceptible to seizures should be only treated with tramadol if there are compelling circumstances.

Tolerance and opioid use disorder (abuse and dependence)
Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Tradol. Repeated use of Tradol can lead to opioid use disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Tradol may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).
Before initiating treatment with Tradol and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.
Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

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

Concomitant use of tramadol and sedative medicines such as benzodiazepines or related medicinal products 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 tramadol 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)

CYP2D6 metabolism
Tramadol 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. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. 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. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1% to 2%

Post-operative use in children
There have been reports in the published literature that tramadol given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life threatening adverse events. Extreme caution should be exercised when tramadol is administered to children for post-operative pain relief and should be accompanied by close monitoring for symptoms of opioid toxicity including respiratory depression.
Children with compromised respiratory function
Tramadol 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.
This medicine contains less than 1 mmol sodium (23 mg) per dose that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Tramadol should not be combined with 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 functions have been observed. The same interactions with MAO inhibitors cannot be ruled out during treatment with tramadol.

Concomitant administration of tramadol with other centrally depressant medicinal products including alcohol may potentiate the CNS effects (see section 4.8).

Sedative medicines such as benzodiazepines or related medicinal products

The concomitant use of opioids with sedative medicines such as benzodiazepines or related medicinal products including gabapentinoids (gabapentin and pregabalin) increases the risk of profound sedation, respiratory depression, hypotension, coma or death because of additive CNS depressant effect. The dose and duration of 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 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 medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of tramadol and serotonergic drugs, 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 syndrome, a potentially life-threatening condition (see sections 4.4 and 4.8)..

Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR, 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).

In a limited number of studies the pre-or postoperative application of the antiemtic 5-HT3 antagonist ondansetron increased the requirements of tramadol in patients with post operative pain.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Tramadol crosses the placenta. There is inadequate evidence available on safety of tramadol in human pregnancy. Therefore tramadol should not be used in pregnant women.

Tramadol-administered before or during birth-does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

Breast-feeding
Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

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

Even when taken according to instructions, tramadol 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

Rapid intravenous administration may be associated with a higher incidence of adverse effects and therefore should be avoided.

The most commonly reported adverse reactions are nausea and dizziness, both occurring in more than 10% of patients.

The frequencies are defined as follows:
very common ≥1/10, common ≥1/100, <1/10), uncommon ≥1/1,000, <1/100), rare ≥1/10,000, <1/1,000), very rare (<1/10,000)
not known: cannot be estimated from the available data.

Cardiac disorders:
Uncommon: cardiovascular regulation (palpitation, tachycardia). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.
Rare: bradycardia

Investigations:
Rare: increase in blood pressure

Vascular disorders:
Uncommon: cardiovascular regulation (postural hypotension or cardiovascular collapse). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.

Metabolism and nutrition disorders
Rare: changes in appetite
Not known: hypoglycaemia

Respiratory, thoracic and mediastinal disorders:
Rare: respiratory depression, dyspnoea
Unknown: hiccups

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section 4.5), respiratory depression may occur.

Worsening of asthma has been reported, though a causal relationship has not been established.

Nervous system disorders:
Very common: dizziness
Common: headache, somnolence
Rare: paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope, speech disorders.
Not known: Serotonin syndrome
Convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicinal products which can lower the seizure threshold (*see sections 4.4 and 4.5*).

Psychiatric disorders:

Rare: hallucinations, confusion, sleep disturbance, delirium, anxiety and nightmares. Psychic adverse reactions may occur following administration of tramadol, 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). Drug dependence may occur. Symptoms of drug withdrawal syndrome, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have very rarely been seen with tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation, paranoia)

Drug dependence
Repeated use of Tradol can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

Eye disorders:
Rare: miosis, mydriasis, blurred vision

Gastrointestinal disorders:
Very common: nausea
Common: vomiting, constipation, dry mouth
Uncommon: retching, gastrointestinal discomfort (a feeling of pressure in the stomach, bloating), diarrhoea.

Skin and subcutaneous tissue disorders:
Common: hyperhidrosis
Uncommon: dermal reactions (e.g. pruritus, rash, urticaria)

Musculoskeletal and connective tissue disorders:
Rare: motorial weakness.

Hepatobiliary disorders:
In a few isolated cases, an increase in liver enzyme values have been reported in a temporal connection with the therapeutic use of tramadol.

Renal and urinary disorders:
Rare: micturition disorders (dysuria and urinary retention)

Immune system disorders
Rare: Allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis

General disorders and administration site conditions:
Common: fatigue

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 HPRA Pharmacovigilance; ebsite: www.hpra.ie

4.9 Overdose

Symptoms
In principle, on intoxication with tramadol symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular miosis, vomiting, cardiovascular collapse, conscious disorders up to coma, convulsions and respiratory depression up to respiratory arrest. Serotonin syndrome has also been reported.

Treatment
The general emergency measures apply. Keep open the respiratory tract (aspiration!) maintain respiration and circulation depending on the symptoms. The antidote for respiratory depression is naloxone. In animal experiments naloxone had no effect on convulsions. In such cases diazepam should be given intravenously.

In case of intoxication orally, gastrointestinal decontamination with activated charcoal or by gastric lavage is only recommended within 2 hours after tramadol intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code : Analgesics NO2AXO2 Other Opioids

Tramadol is a centrally acting opioid analgesic. It is a non selective pure agonist at microgram, δ and κ opioid receptors with a higher affinity for the microgram 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 more than 2000 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 found to be superior to placebo, and superior or equal to paracetamol, nalbuphine, pethidine or low dose morphine. The conducted trials confirmed the efficacy of tramadol. The safety profile of tramadol was similar in adult and paediatric patients older than 1 year (see section 4.2).

5.2 Pharmacokinetic properties

After intramuscular administration in humans, tramadol is absorbed rapidly and completely: the mean peak serum concentrations (Cmax) is reached after 45 minutes and bioavailability is almost 100%.

The half-life of the terminal elimination phase (t½, ß) is 6.0 ± 1.5 h in young volunteers.
Tramadol pharmacokinetics show little age-dependence, the minimal changes being therapeutically irrelevant. In patients above the age of 65 years the t½, ß was 6.5 ± 1.7 h on oral administration. Since tramadol is eliminated both metabolically and renally, the terminal half-life t½, ß may be prolonged in impaired hepatic or renal function.

However, the increase in the t½, ß values is relatively low if at least one of these organs is functioning normally. In patients with liver cirrhosis t½, ß Tramadol was a mean of 13.3 ± 4.9 h, in patients with renal insufficiency (creatinine clearance < 5 ml/min) it was 11.0 ± 3.2 h.

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.

Paediatric population

The pharmacokinetics of tramadol and O-desmethyltramadol after single-dose and multiple-dose oral administration to subjects aged 1 year to 16 years were found to be generally similar to those in adults when adjusting for dose by body weight, but with a higher between-subject variability in children aged 8 years and below.

In children below 1 year of age, the pharmacokinetics of tramadol and O-desmethyltramadol has been investigated, but has not been fully characterised. Information from studies including this age group indicates that the formation rate of O-desmethyltramadol via CYP2D6 increases continuously in neonates, and adult levels of CYP2D6 activity are assumed to be reached at about 1 year of age. In addition, immature glucuronidation systems and immature renal function may result in slow elimination and accumulation of O-desmethyltramadol in children under 1 year of age.

5.3 Preclinical safety data

On repeated oral parenteral administration of tramadol for 6-26 weeks in rats and dogs and oral administration for 12 months in dogs haematological, clinicochemical and histological investigations showed no evidence of any substance-related changes. Central nervous manifestations only occurred after high doses considerably above the therapeutic range: restlessness, salivation, convulsions, and reduced weight gain. Rats and dogs tolerated oral doses of 20mg/kg and 10mg/kg body weight respectively, and dogs rectal doses of 20mg/kg body weight without any reactions.

In rats tramadol dosages from 50 mg/kg/day upwards caused toxic effects in dams and raised neonate mortality. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male fertility was not affected. After higher doses (from 50 mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects in dams from 125 mg/kg upwards and skeletal anomalies in the offspring.
In some *in vitro* test systems there was evidence of mutagenic effects. *In vivo* studies showed no such effects. According to knowledge gained so far, tramadol can be classified as non-mutagenic.

Studies on the tumourigenic potential of tramadol hydrochloride have been carried out in rats and mice. The study in rats showed no evidence of any substance-related increase in the incidence of tumours. In the study in mice there was an increased incidence of liver cell adenomas in male animals (a dose-dependent, non-significant increase from 15 mg/kg upwards) and an increase in pulmonary tumours in females of all dosage groups (significant, but not dose-dependent).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Acetate Trihydrate
Water for Injection

6.2 Incompatibilities

Precipitation will occur if TRADOL injection is mixed in the same syringe with injections of diazepam, non-steroidal anti-inflammatory drugs and anion-forming drugs.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

Unopened: 3 years.
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C with the infusion fluids listed in section 6.6
From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25°C.

For storage conditions of the opened, diluted or reconstituted medicinal product, see section 6.3

6.5 Nature and contents of container

TRADOL Injection is contained in 1 ml ampoules or 2 ml ampoules of colourless neutral Type I Ph. Eur. glass.
TRADOL Injection will be available in packs of 5 ampoules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C with the following infusion fluids.

0.9% Sodium Chloride.
0.18% Sodium Chloride and 4% Glucose
5% Glucose
Haemaccel

For single use only.

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

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/029/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 25th June 2009

10 DATE OF REVISION OF THE TEXT

December 2024