SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PRİCAİN 2% SOLUTION FOR I.V. INJECTION

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each ml of vial contains 20.0 mg Prilocaine hydrochloride

Excipients:

Sodium chloride 6 mg/ml

Methyl parahydroxybenzoate (E218) 1 mg/ml

Electrolyte concentrations (per liter):

Sodium: 105 mEq = 105 mmol

Chloride: 180 mEq= 180 mmol

See Section 6.1 for other excipients.

3. PHARMACEUTICAL FORM

Vial containing solution for injection.

PRİCAİN is sterile, apyrogen, isotonic, aqueous injectable colorless non-particle solution.

pH of solution about 5-7. Contains methyl parahydroxybenzoate as preservative.

4. CLINICAL PARTICULARS

4.1. Therapeutical indications

PRİCAİN is indicated local or regional anesthesia using the following techniques.

- Local infiltration
- Small and large nerve blocks
- Epidural block
- Arthroscopy, intravenous regional anesthesia

4.2. Posology and method of administration

Adults and children above 12 years of age:

Posology/ Frequency and period of administration:
The following table of average for an adult dosage to be administered more frequently used technique is intended as a guide. Values reflect the expected average dose range needed. Factors affecting specific block techniques and standard sources should be consulted for individual patient needs.

The calculation of the required dose, the experience of physician and the physical condition of the patient are important. The lowest dose required for adequate anesthesia should be used. (See Section 4.4.). Individual variability can be seen at the beginning and during the treatment (see. Table 1).

Table 1. Dose advices

Type of block	Concentration mg/ml	Dose		Time of beginning to effect (min)	Action time (hour)
		ml	mg		
SURGICAL ANESTHESIA					
Lumbar Epidural Administration [a)]	20	15-25	300-500	15-20	1.5-2
Thoracic Epidural Administration [a)]	20	10-15	200-300	10-20	1.5-2
Caudal Epidural Block [a)]	10 20	20-30 15-25	200-300 300-500	15-30 15-30	1-1.5 1.5-2
IV regional (Bier block) a. Upper extremity [b)] b. Lower extremity [b)] i) Femoral tourniquet ii) Calf tourniquet	 5 5 5	 40 60 40	 200 300 200	 10-15 10-15 10-15	Until tourniquet unfasten -"- -"-
Intra- articular block [c)]	5 10	≤ 60 ≤ 40	≤ 300 ≤ 400	5-10 5-10	After wash-out 30-60 min.
Region Block (e.g. Small nerve blocks and infiltration)					
Infiltration	5 10	≤ 100 ≤ 50	≤ 500 ≤ 500	1-2 1-2	1.5-2 2-3
Digital block [d)]	10	1-5	10-50	2-5	1.5-2
Intercostal (to nerve head) Max. blocked nerve count should be ≤ 10 at the same time	10	2-5	20-50	3-5	1-2
Retrobulbar [d)] Peribulbar [d)]	20 10	4 10-15	80 100-150	3-5 3-5	1.5-2 1.5-2
Major nerve block					
Brachial plexus: Axillary supraclavicular, Interscalen and subclavian perivasculary	 10 10	 40-50 30-40	 400-500 300-400	 15-30 15-30	 1.5-2 1.5-2
Sciatica	20	15-20	300-400	15-30	2-3
Triple block (Femoral, obturator and lateral cutaneous)	10	30-40	300-400	15-30	1.5-2

Note:
[a)] Dose includes test dose.
[b)] Tourniquet should not unfasten during 20 minutes after injection.
[c)] There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anesthetics. PRİCAİN is not approved for this indication.
[d)] Doses given without epinephrine.
≤ = till

Preservative containing solutions i.e. those supplied in multi-dose vials should not be used for intrathecal or epidural anesthesia, intraocular or retro bulbar injections. Repeated and continious administration should be avoided in case of epidural applications.

Surgical anesthesia generally (e.g. Epidural) requires the using of higher concentrations and doses. Using a lower dose is effective when needed less deep block. The amount of drug used will affect the spreading width of the anesthesia.

Route of administration:
Avoid to intravascular injection, vital functions of patients closely observing and the main dose should be injected with verbal communication with the patient slowly or 100-200 mg/min before applying an increased dose rate during the application and must be repeated aspiration process. The short-acting local anesthetic containing a dose of adrenaline is going to be injected into the epidural is recommended to apply a pre-test dose of 3-5 ml. Made intravascular injection by accident can be realized by a transient increase in heart rate. If toxic symptoms develop, the injection should be stopped immediately.

Special populations:
Renal /hepatic impairment:
See section 4.4. for warning to using patients with renal and hepatic impairment.

Pediatric population:
Dose in Table 2 should be seen as a guide for pediatric patients. Individual variations occur. Body weight a gradual reduction of the dose in children is often more necessary and should be based on ideal body weight. Factors affecting specific block techniques and standard sources should be consulted for individual patient needs.

Table 2. Dose advises for children

	Contantration mg/ml	Volume ml/kg	Dose mg/kg	Time of beginning to effect (min)	Action time (hour)
Caudal epidural	10	0.5	5	10-15	1-1.5

Age and weight should be taken into account for the calculation of dose.
Preservative containing solutions i.e. those supplied in multi-dose vials should not be used for intrathecal or epidural anesthesia, intraocular or retro bulbar injections.

Prilocaine injection should not be used in children under 6 months of age and for use in paracervical (PCB) block and pudendal block in the obstetric patient. There is an increased risk of methaemoglobin formation in children and in the neonate after delivery (see section 4.8).

Geriatric population:
See section 4.4. for warning to using elderly patients.

4.3. Contraindications
PRİCAİN is contraindicated in;

- Hypersensitivity to the active substance, anesthetics of the amide type or to any of the excipients,
- Hypersensitivity to methyl and/or propyl parahydroxybenzoate (methyl-/propyl paraben), or to their metabolite para-amino benzoic acid (PABA),
- Formulations of prilocaine containing parabens should be avoided in patients allergic to ester local anesthetics or its metabolite PABA.
- Patients with anemia or congenital or acquired methaemoglobinaemia.

4.4. Special warnings and precautions for use
Regional anesthetic procedures should always be performed in a properly equipped and staffed area, with the equipment and drugs necessary for monitoring an emergency resuscitation immediately available.

Great caution must be exercised to avoid accidental intravascular injection of this compound, since it may give rise to the rapid onset of toxicity, with marked restlessness, twitching, or convulsions, followed by coma with apnoea and cardiovascular collapse.

When performing major blocks, an i.v. cannula should be inserted before the local anesthetic is injected. Clinicians should have received adequate and appropriate training in the procedure to be performed and should be familiar with the diagnosis and treatment of side effects, systemic toxicity or other complications (see section 4.9).

Some patients require special attention in order to reduce the risk of serious undesirable effects, even when loco regional anesthesia constitutes the optimum choice for the surgical intervention:

- Elderly patients and patients in reduced general condition.
- Patients with total or partial heart block, since local anesthetics can suppress myocardial conduction.
- Patients with advanced liver or kidney damage.

- Patients with high grade cardiac decompensation. The risk of methemoglobinemia must also be taken into consideration (see section 4.8).
- Patients treated with class III antiarrhythmic agents (e.g. amiodarone). These patients should be subjected to careful observation and ECG monitoring, since cardiac effects may be added (see section 4.5).
- In patients with acute porphyria, PRİCAİN should only be administered when there is a compelling indication for its use, as PRİCAİN may potentially precipitate porphyria. Appropriate precaution should be taken in all patients with porphyria.

Important note: Using prilocaine is not recommended children younger than 6 months.
Prilocaine is not recommended for paracervical block (PCB) or pudendal block in the obstetric patient hence risk of development of methaemoglobinaemia in infants (see sections 4.2 and 4.8 "methaemoglobinaemia").

Certain local anesthetic procedures may be associated with serious adverse reactions, regardless of the local anesthetic drug used, e.g.:

- Central nervous blocks, may cause cardiovascular depression especially present hypovolemia. Therefore, epidural anesthesia should be used with caution in patients with cardiovascular functions inadequate.
- Retro bulbar injections (rarely) reach the cranial subarachnoid space may cause temporary blindness, cardiovascular collapse, apnea and convulsions.
- Retro- and per bulbar injections of local anesthetics carry a low risk of persistent ocular muscle dysfunction. The primary causes include trauma and/or local toxic effects on muscles and/or nerves. The severity of such tissue reactions is related to the degree of trauma, the concentration of the local anesthetic and the duration of exposure of the tissue to the local anesthetic. For this reason, as with all local anesthetics, the lowest effective concentration and dose of local anesthetic should be used. Vasoconstrictors and other additives may aggravate tissue reactions and should be used only if indicated.
- Injections in the head and neck regions may be made inadvertently into an artery, causing cerebral symptoms even at low doses.
- There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anesthetics. The majority of reported cases of chondrolysis have involved the shoulder joint. Due to multiple contributing factors and inconsistency in the scientific literature regarding mechanism of action, causality has not been established. Intra-articular continuous infusion is not an approved indication for PRİCAİN.
- Para cervical block can cause fetal bradycardia/tachycardia sometimes. Therefore, careful monitoring of fetal heart rate is necessary.
- Methaemoglobinaemia may occur at lower doses of prilocaine in patients suffering from anemia, from congenital or acquired haemoglobinopathy (including

methaemoglobinaemia), or in patients receiving concomitant therapy e.g. sulphonamides, known to cause such conditions. Infants are particularly susceptible, due to a lower activity of the enzyme which reduces methaemoglobin to haemoglobin. Hence prilocaine is not recommended for para cervical block (PCB) or pudendal block in the obstetric patient and in children under the age of 6 months.

- Local anesthetics should be avoided when there is inflammation at the site of the proposed injection.

Epidural anesthesia may cause hypotension and bradycardia. This risk can be reduced by circulation preload with crystalloid or colloidal solutions. Hypotension should be treated promptly with a sympathomimetic intravenously and should be repeated as necessary.

Preservative containing solutions i.e. those supplied in multi-dose vials should not be used for intrathecal or epidural anesthesia, intraocular or retro bulbar injections.

This medicinal product contains 0.105 mmol sodium per 1 ml. This should be considered for patients on a controlled sodium diet.

Methylparahydroxybenzoate can cause allergic reactions (possibly delayed) and exceptionally bronchospasm.

4.5. Interactions with other medical products and other forms of interaction

Prilocaine should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type anesthetics, since the toxic effects are additive.
Specific interaction studies with prilocaine and anti-arrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution is advised (see also section 4.4).
Drugs which may predispose to methaemoglobin formation, e.g. sulfonamides, antimalarial and certain nitric compounds, could potentiate this adverse effect of prilocaine.

Special populations

Geriatric population:

Caution should be taken when using in geriatric population.

Pediatric population:

Should not use in children younger than 6 months.

4.6. Pregnancy and lactation

General

Pregnancy category: B

Women with potential of giving birth /Contraception
No sufficient clinical data is available for the use of PRİCAİN in pregnant women.

Pregnancy

When used above 600 mg in obstetric anesthesia, prilocaine metabolites can cause clinically significant methemoglobinemia in mother and infants.

Neonatal methaemoglobinaemia has been reported after paracervical block (PCB) or pudendal block in the obstetric patient.

Fetal adverse effects due to local anesthetics, such as fetal bradycardia, seem to be most apparent in Para cervical block anesthesia. Such effects may be due to high concentrations of anesthetic reaching the fetus.

Caution should be exercised when giving to pregnant women. It should not be used unless it is necessary. Although there is no evidence of harmful effects on the fetus in animal experiments, PRİCAİN should not be used in early pregnancy (unless its benefit is superior to its harm).

Lactation

It is not known to what proportion of prilocaine excrete to breast milk. However, the breastfed infants receive prilocaine that may be considered to be minimal.

Reproductive capability/Fertility

Drug-related adverse effects were not observed in reproductive toxicity studies (See Section 5.3).

4.7. Effects on ability to drive and use machines

Besides the direct anesthetic effect, local anesthetics may have a very mild effect on mental function and co-ordination even in the absence of overt CNS toxicity, and may temporarily impair locomotion and alertness.

4.8. Undesirable effects

General
The adverse reaction profile for PRİCAİN is similar to those of other amide local anesthetics. Adverse reactions caused by the drug *per se* are difficult to distinguish from the physiological effects of the nerve block (e.g. decrease in blood pressure, bradycardia), events caused directly (e.g. nerve trauma) or indirectly (e.g. epidural abscess) by the needle puncture.

Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10.000 and <1/1000);

Vascular disorders

Very common: hypotension*

Common: hypertension

Gastrointestinal disorders

Very common: nausea*

Common: vomiting*

Nervous system disorders

Common: paraesthesia, dizziness

Uncommon: signs and symptoms of CNS toxicity (convulsions, circumoral paresthesia, loss of consciousness, shaking, feeling of numbness affecting the tongue, speech problems, hearing problems, tinnitus, visual problems) (see section 4.8 “Acute systemic toxicity” and section 4.9)

Rare: Neuropathy, lesions of peripheral nerves, arachnoiditis

Cardiac disorders

Common: Bradycardia

Rare: Cardiac arrest, cardiac arrhythmias

Immune system disorders

Rare: Allergic reactions, anaphylactic reactions, urticaria, oedema, dyspnoea

Respiratory, thoracic and mediastinal disorders

Rare: Respiratory depression

Eye disorders

Rare: Acute diplopia

Blood and lymphatic system disorders

Rare: methaemoglobinaemia (see section 4.9), cyanosis**

*Developed adverse drug reactions more frequently after the epidural block.

**In the presence of methemoglobinemia

Acute systemic toxicity:

Systemic toxic reactions primarily involve the central nervous system (CNS) and the cardiovascular system. Such reactions are caused by high blood concentrations of a local anesthetic, which may appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularized areas (see section 4.4). CNS reactions are similar for all amide local anesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively.

Central nervous system, toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are circumoral paranesthesia, numbness of the tongue, light-headedness, hyperacusis, tinnitus and visual disturbances. Dysarthria, muscular twitching or tremors are more serious and precede the onset of generalized convulsions. These signs must not be mistaken for neurotic behavior. Unconsciousness and grand mal convulsions may follow which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with respiration and possible loss of functional airways. In severe cases apnea may occur. Acidosis, hyperkaliemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anesthetics.

Recovery is due to redistribution of the local anesthetic drug from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the drug have been injected.

Cardiovascular system toxicity may be seen in severe cases and is generally preceded by signs of toxicity in the central nervous system. In patients under heavy sedation or receiving a general anesthetic, prodromal CNS symptoms may be absent. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anesthetics, but in rare cases cardiac arrest has occurred without prodromal CNS effects.

In children, early signs of local anesthetic toxicity may be difficult to detect in cases where the block is given during general anesthesia.

Treatment of acute toxicity

If signs of acute systemic toxicity appear, injections of the local anesthetic should be stopped immediately and CNS symptoms (convulsion, CNS depression) must promptly be treated with appropriate airway/respiratory support and the administration of anticonvulsant drugs.

If circulatory arrest should occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

If cardiovascular depression occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, chronotropic and or inotropic agents should be considered. Children should be given doses commensurate with age and weight.

Methaemoglobinaemia

Methaemoglobinaemia may occur after the administration of prilocaine. The repeated administration of prilocaine, even in relatively small doses, can lead to clinically overt methaemoglobinaemia (cyanosis). Prilocaine is therefore not recommended for continuous techniques of regional anesthesia.

is a metabolite of prilocaine which have a long half-life and tent to accumulate accumulation, cause the conversion of hemoglobin into methemoglobin, changing the order of 4- and 6-hidroksitoluid.

Methaemoglobin has risen to clinically significant levels in patients receiving high doses of prilocaine. Cyanosis occurs when the methaemoglobin concentration in the blood reaches 1–2 g/100 ml (6–12% of the normal haemoglobin concentration). Although oxidized methemoglobin to hemoglobin very slow process, administered intravenously with methylene blue can be accelerated substantially. (See Section 4.8. "Treatment of Methaemoglobin").

The reduction in oxygen-carrying capacity due to the administration of prilocaine in normal patients is marginal; hence the methaemoglobinaemia is usually symptomless. However, in severely anaemic patients it may cause hypoxaemia. It is important to rule out other more serious causes of cyanosis such as acute hypoxaemia and/or heart failure.

In neonates and small infants there is an increased risk of development of methaemoglobinaemia (see sections 4.2 and 4.4).

Note: Even low concentrations of methaemoglobin may interfere with pulse oximetry readings, indicating a false, low oxygen saturation.

Treatment of methaemoglobinaemia

If clinical methaemoglobinaemia occurs, it can be rapidly treated by a single intravenous injection of a 1% methylene blue solution, 1 mg/kg body weight, over a 5-minute period. Cyanosis will disappear in about 15 minutes. This dose should not be repeated as methylene blue in high concentrations acts as a haemoglobin oxidant.

4.9. Overdosage

Accidental intravascular injections of local anesthetics may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, systemic toxicity appears later (15–60 minutes after injection) due to the slower increase in local anesthetic blood concentration (see section 4.8 Acute systemic toxicity and Treatment of acute systemic toxicity).

5. PHARMACOLOGIC PROPERTIES

5.1. Pharmacodynamic properties

Pharmacoterapeutical group: Anesthetics, local,

ATC code: N01BB04

Prilocaine hydrochloride (PRİCAİN) is a local anesthetic of the amide type. The onset time, duration of action and power are similar to lidocaine. The 2% solution will last up to 4 hours with peripheral nerve blocks. When used in concentrations of 1%, there is less effect on motor nerve fibers and the duration of action is shorter. Peak plasma concentration of prilocaine at the same dose lower than lidocaine and eliminated faster. Prilocaine has lower acute toxicity than lidocaine.

Onset and the duration of the local anaesthetic effect of prilocaine depend on the dose and the site of administration. However, its propensity for causing methaemoglobinaemia makes it unsatisfactory for continuous techniques.
Local anesthetics act by preventing transmission of impulses along nerve fibers and at nerve endings; depolarization and ion-exchange are inhibited. The effects are reversible. Nerve membranes sodium channels, are regarded as a receptor for local anesthetic molecules.

Local anesthetic drugs may have similar effects on other excitable membranes such as the brain and myocardium. If a large amount of drug exceeds the systemic circulation substantially central nervous system and cardiovascular system the toxicity signs and symptoms occur.

Central nervous system toxicity occurs at lower plasma concentrations. (See Section 4.8) and cardiovascular effects usually seen before. Transmission between the direct effects of local anesthetics on the heart to slow down, negative inotropic effect and finally cardiac arrest.

After epidural administration concomitant sympathetic block, depending on the degree of indirect impacts cardiovascular (hypotension, bradycardia) may occur.

5.2. Pharmacokinetic properties

General characteristics

pKa of prilocaine is 7.89 and partition constant of N-heptane/pH 7.4 tampon is 0.9. Prilocaine has 25 octanol/water ratio in pH 7.4.

Absorption:

The peak plasma concentration after prilocaine administration depends on the dose, the route of administration, vascularity of the injection site and the concomitant administration of vasoconstrictor agents.

Maximum plasma concentrations occur after intercostal nerve block. Decrease as compared to others, injections applied to the lumbar epidural space, large nerve blocks such as brachial plexus and the subcutaneous injection.

Reason of maximum plasma concentrations were observed intercostal applications following is necessary a large number of injection technique, spread over a larger area of the vascular solution and absorption faster accordingly. On the other hand, adipose tissue in the lumbar epidural space, will tend to slowdown vascular absorption.

Distribution:

Prilocaine has 2.37 l/min, a mean plasma clearance, large apparent volume of distribution from 190 liters to 260 liters. The terminal half-life of prilocaine is 1.6 hours. Plasma protein binding rate is 40% (mainly alpha-s - acid glycoprotein).

Biotransformation:

In the liver, prilocaine is primarily metabolised by amide hydrolysis to orthotoluidine and N-propylamine. O-Toluidine is subsequently hydroxylated to 2-amino-3-hydroxytoluene and 2-amino-5-hydroxytoluene, metabolites with long half-lives that tend to accumulate and are believed to be responsible for the occurrence of methaemoglobinaemia. *In vitro* research and studies conducted on animals showed that of prilocaine are metabolized in the liver and kidney tissue.

Elimination:

A small proportion of prilocaine (<5%) is excreted unchanged in the urine.

Linearity/non-linearity:

The quantity of prilocaine administration 200-600 mg dose has a linear relationship between the peak plasma concentrations.

Easily it passes through the placenta and prilocaine is in terms of rapidly achieving equilibrium concentration of unbound. If fetal acidosis may be higher concentrations in the fetus. Newborns have no information about the elimination half-life of prilocaine.

It is uncertain the impact of diseases such as severe liver cirrhosis and congestive heart failure to distribution of prilocaine.

5.3. Preclinic safety data

In animal studies, the symptoms and signs of toxicity noted after high doses of prilocaine are the results of the effects on the central nervous and cardiovascular systems. A mild methaemoglobinaemia was seen in a single study in rats, after repeated dosing. This is also occasionally seen in the therapeutic situation as a result of prilocaine overdose or off-label use. No drug related adverse effects were seen in reproduction toxicity studies, neither did prilocaine show mutagenic potential in either in vitro or in vivo mutagenicity tests. Cancer studies have not been performed with prilocaine due to the indication and duration of therapeutic use of this drug.

The main metabolite of prilocaine, o-toluidine, has been shown to be genotoxic and is also carcinogenic in preclinical toxicological studies evaluating chronic exposure. As a result of intermittent use of prilocaine calculated maximum exposure to the risk assessment report, which compared the use of exposure results in preclinical studies, indicate that a wide range of safety in clinical use.

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Sodium chloride

Sodium hydroxide/hydrochloric acid

Methyl parahydroxybenzoate (E218)

Water for injection

PRİCAİN injections are sterile isotonic aqueous solutions. Single-dose vials and ampoules, does **not contain a preservative and is for single use only**. Multi-dose vials contain preservatives.

6.2. Incompatibilities

The resolution of the prilocaine is limited in the pH with greater than 7.0. Precipitation may occur, is considered as the addition of alkaline carbonate solution should be considered in this case.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Keep at room temperature under 25°C.

Do not freeze.

6.5. Nature and contents of container

20 ml, type I amber color glass vials with PP flip-off caps and Al hoods placed rubber stops.

6.6. Special precautions for disposal

The unused products and waste materials must be destructed according to the local regulations.

Microbial contamination risk of multi-dose vials are more than disposable vial. Therefore, single-dose vials to be used wherever possible. When multi-dose vials used, appropriate control actions must be made including below to avoid contamination.

-The use of disposable sterile injection equipment

- A sterile needle and syringe be used for each entry

- Fluid or contaminated substance has been preventing entry into a multiple-dose vial containing

- The multiple vials containing doses should not be used by more than 3 days after opening the vial.

PRİCAİN is not recommended to re-sterilization.

7. MARKETING AUTHORISATION HOLDER

POLİFARMA İLAÇ SAN. VE TİC. A.Ş

Vakıflar OSB Mahallesi, Sanayi Caddesi, No: 22/1,
Ergene/Tekirdağ/TURKEY

8. MARKETING AUTHORISATION NUMBER(S)

2014/763

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 26/09/2014
Renewal of the Authorisation: 05/12/2019

10. DATE OF REVISION OF THE TEXT

17/10/2019