SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See Section 4.8 for how to report adverse reactions

1 NAME OF THE MEDICINAL PRODUCT

Trobigard Auto-injector, 2 mg / 220 mg solution for injection in pre-filled pen.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The pre-filled injector contains 2 mL of solution as a fixed-dose combination of two active ingredients:

- Atropine sulfate 1 mg/mL delivering a single dose of 2 mg
- Obidoxime chloride 110 mg/mL delivering a single dose of 220 mg

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in a pre-filled pen

Clear yellow solution with a pH of 2.6 – 4.2.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The Trobigard Auto-injector is indicated for the emergency treatment of known or suspected exposure to nerve agents or toxic organophosphates in adults >18 years of age.

4.2 Posology and method of administration

The use of this emergency treatment should be restricted to trained personnel, after recognising the symptoms of potential poisoning with organophosphate nerve or toxic agents.

Posology

For intramuscular use only.

The medicinal product is intended for single use. The injection can be administered through clothing.

Self-administration: Use the auto-injector immediately after recognising the effects of potential poisoning with organophosphate nerve or toxic agents such as unexplained runny nose/salivation/tearing, tightness of chest with difficult breathing, blurred vision, pupils constricted, nausea, vomiting, abdominal cramps, involuntary urination/defecation, involuntary jerking/twitching/cramps, staggering, headache, drowsiness, and/or convulsions.

If symptoms persist after administering the first auto-injection, a second auto-injection should be administered, to a maximum of 3 auto-injections.

First aid by others: For those who cannot self-administer the auto-injection and who show toxic effects listed above (see Self-administration section) or are in a coma or have undergone respiratory arrest, administer the auto-injection(s), as described in the Self-administration section, up to a maximum of 3 auto-injections.

Medical Assistance: Individuals or those administering first aid to individuals who believe they have been exposed to a nerve agent should follow appropriate government-use procedures and seek medical attention after administering Trobigard Auto-injector.

Paediatric population

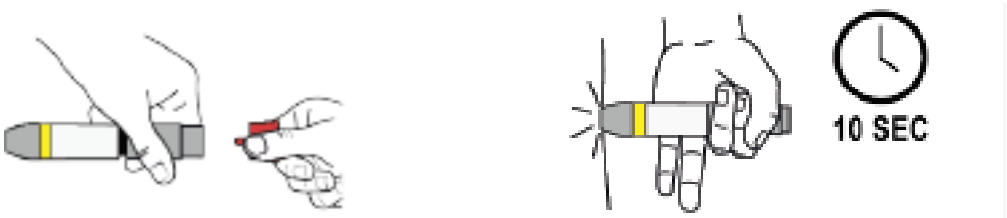
The safety and efficacy of the Trobigard Auto-injector in children <18 years of age has not been established.

Method of administration

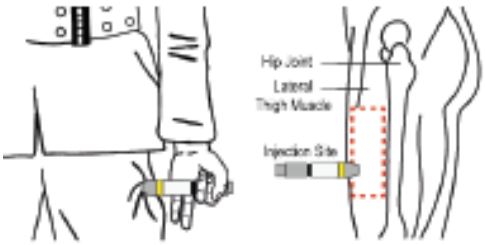
Inject the dose within the Trobigard Auto-injector into the anterolateral (outer) aspect of the thigh, through clothing, if necessary.

The Trobigard Auto-injector is used as follows:

1. Remove the red device lock. Grip the grey top part of the auto-injector only.
2. Press the auto-injector hard on the outer thigh until the injector functions (clicks).
3. Hold firmly in place for 10 seconds.



For self/first-aid/buddy administration, administer into the injection site as shown below:



A single dose may not be sufficient to antagonise the effects of cholinergic overstimulation. Therefore, wait a few minutes to assess whether there is improvement in the symptoms. If there is no/limited improvement, then administer a second auto-injection. If there is still no improvement, a third auto-injection may be administered. In severe cases of exposure to nerve agents, three auto-injections may be given simultaneously.

See Section 6.6 for information regarding disposal.

4.3 Contraindications

In the face of life-threatening symptoms due to nerve agent or organophosphate poisoning, there are no absolute contraindications to the emergency use of the Trobigard Auto-injector as the benefits of its administration in such situations outweigh the potential negative effects that may occur.

4.4 Special warnings and precautions for use

Use only as an initial emergency treatment in cases of known or suspected nerve agent or organophosphate poisoning. In addition to use of the product, definitive medical care should be sought immediately to aid treatment of clinical symptoms, including decontamination and transfer to a medical facility.

While an allergic reaction to the active ingredients (see Section 2) and/or the excipients (see Section 6.1) of this medicine is possible, use of the auto-injector is not contraindicated in life-threatening situations.

The auto-injector should not be used if the symptoms of poisoning have been present for more than 24 hours, as its intended use is emergency treatment only.

Caution: The device should be kept in the packaging until you are ready to use it to prevent accidental removal of the red safety cap. The cap unlocks the device for activation. Do not remove the cap until you are ready to perform an injection.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed in humans. Based on the non-clinical data, no evidence of relevant drug interactions between atropine and obidoxime is expected (see Section 5.3)

4.6 Fertility, pregnancy and lactation

Pregnancy:

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicated no malformative or feto/neonatal toxicity of atropine. Animal studies have shown reproductive toxicity (see Section 5.3).

There are no or limited amount of data from the use of obidoxime in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (See Section 5.3).

As a precautionary measure, it is preferable to avoid using Trobigard Auto-injector during pregnancy unless in life-threatening situations where there has been possible exposure to chemical nerve agents or organophosphate poisons where the benefit outweighs the risks (see Section 4.3).

Lactation:

Atropine/metabolites are excreted in human milk and effects have been shown in breastfed newborns/infants of treated mothers (See Section 5.3)

It is not known whether obidoxime/metabolites are excreted in human milk.

The Trobigard Auto-injector should only be used in lactating females in life-threatening situations where there has been possible exposure to chemical nerve agents or organophosphate poisons where the benefit outweighs the risk to the infant (see Section 4.3).

Fertility:

Atropine is known to impair male fertility in animal studies (see Section 5.3). It is not known whether obidoxime/metabolites impact fertility.

The Trobigard Auto-injector should only be used in life-threatening situations where there has been possible exposure to chemical nerve agents or organophosphate poisons where the benefit outweighs the risk (see Section 4.3).

4.7 Effects on ability to drive and use machines

No special restrictions or precautions this preparation is intended for use only in emergency situations.

4.8 Undesirable effects

There are no clinical trial data available for the fixed-dose combination product (Atropine sulfate / Obidoxime chloride co-formulation) which would allow estimation of frequency of adverse reactions with Trobigard Auto-injector.

Tabulated list of adverse reactions:

As no information is available for the Trobigard Auto-injector, the information in Table 1 is taken from known adverse reactions reported individually for atropine and for obidoxime. 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, including isolated reports
Not known:	Cannot be estimated from the available data

Table 1 Adverse Reactions Reported from Literature for Atropine sulfate and Obidoxime chloride

System Organ Class	Atropine sulfate injection		Obidoxime chloride injection	
	Adverse Reactions	**Frequency**	**Adverse Reaction**	**Frequency**
Psychiatric disorders	Insomnia, Nervousness	Not known		
	Restlessness, Agitation, Confusion, Excitement, Hallucinations (especially with higher dosages). Delirium	Common		

System Organ Class	Atropine sulfate injection		Obidoxime chloride injection	
	Adverse Reactions	**Frequency**	**Adverse Reaction**	**Frequency**
	Psychotic reactions	Uncommon		
Nervous system disorders	Numbness (hypoaesthesia), Headache, Dizziness, Ataxia (impaired locomotor coordination)	Not known	Dysgeusia (taste of menthol)	Not known
	Unconsciousness, Memory disorders, Concentration disorders, Incoordination	Common		
	Seizure, Drowsiness	Rare		
Eye disorders	Accommodation paralysis with disturbance of the near vision	Common		
	Visual disturbances: Mydriasis (pupil dilation), Inhibition of accommodation, Blurred vision, Photophobia	Very common		
	Increased ocular tension	Not known		
Cardiac disorders	Acute myocardial infarction[1]	Not known	Cardiac arrhythmia	Not known
	Tachycardia, Arrhythmias, Transient exacerbation of bradycardia	Common		
	Atrial arrhythmias, Ventricular fibrillation, Angina, Hypertensive crisis	Very rare		
Vascular disorders	Flushing	Common		
Gastrointestinal disorders	Reduction of salivary secretions, Dryness of the mouth (dry mouth), Difficulty in swallowing (dysphagia), Difficulty talking, Thirst, Parasympathetic inhibition of gastrointestinal tract (constipation and reflux) Inhibition of gastric secretion, Loss of taste, Nausea, Vomiting, Bloated feeling	Very common	Dry mouth	Not known
Hepatobiliary disorders			Jaundice cholestatic[2], Hepatic function abnormal[3], Elevated liver enzymes, Temporary “liver function disorders”	Not known
Immune system	Allergic reactions	Rare		
	Anaphylaxis	Very rare		
Investigations			Electrocardiogram change, Heart rate increased, Blood pressure increased, Blood pressure drop	Not known
Renal and urinary	Inhibition of the parasympathetic control of the urinary bladder,	Common		

System Organ Class	Atropine sulfate injection		Obidoxime chloride injection	
	Adverse Reactions	Frequency	Adverse Reaction	Frequency
disorders	Urinary retention			
Respiratory, thoracic and mediastinal disorders	Reduced bronchial secretion[4]	Very common		
Skin and subcutaneous tissue disorders	Redness (with flushing)	Not known		
	Anhidrosis, Urticaria, Rash	Very common		
Musculoskeletal and connective tissue disorders	Muscular weakness	Not known	Muscular weakness	Not known
General disorders and administration site conditions	Hyperthermia	Common	Feeling hot, Feeling cold, Cold sensitivity	Not known

[1] Large doses block vagal impulses with consequent increase in heart rate with possible atrial arrhythmias, A-V dissociation and multiple ventricular ectopic beats, ST-elevation, acute myocardial infarction.
[2] With doses exceeding 3000-10000 mg within 1-3 days
[3] With doses exceeding 2000 mg
[4] May cause dehydration of residual secretion and formation of thick bronchial plugs that are difficult to eject out of respiratory tract.

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:

Federaal agentschap voor geneesmiddelen en gezondheidsproducten Afdeling Vigilantie /
Agence fédérale des médicaments et des produits de santé Division Vigilance /
Föderalagentur für Arzneimittel und Gesundheitsprodukte Abteilung Vigilanz

Avenue Galilée - Galileelaan 5/03 1210 BRÜSSEL	Postfach 97 1000 BRÜSSEL

Website: www.notifieruneffetindesirable.be
e-mail: adr@afmps.be

4.9 Overdose

There is no data on overdose with use of the Trobigard Auto-injector. Due to the limited number of Trobigard Auto-injectors allocated for “self” (1-3 injectors) and “buddy” (1-3 injectors) administration, overdose is unlikely. However, the improper or accidental administration of the Trobigard Auto-injector may result in a higher than recommended dose of atropine and/or obidoxime being administered; consequently, the undesirable effects listed for atropine and obidoxime separately under Section 4.8 may be more pronounced.

Management:

In case of overdose, physostigmine, 1 to 4 mg, should be administered intravenously, intramuscularly or subcutaneously. The dose may be repeated, if necessary, since it is rapidly eliminated from the body. Diazepam 10 to 20 mg may be administered for sedation of a delirious patient. An adequate airway should be maintained, and respiratory failure should be promptly treated with standard emergency procedures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidote, ATC code: V03AB

Mechanism of action

Trobigard Auto-injector combines two active ingredients; Atropine sulfate and Obidoxime chloride, to counteract the effects of organophosphate nerve (OP) agent exposure/poisoning.

Atropine is a competitive inhibitor of ACh for the orthosteric ACh site on muscarinic receptors found in the peripheral and central nervous systems (CNS).

Obidoxime's principal mechanism of action is to reverse the binding of OP compounds to the AChE and reactivate the cholinesterase enzyme, for as long as reactivation is possible (aging). Oximes, which are nucleophilic substances reactivate normal AChE function by removing the phosphyl moiety at the active center of the enzyme and restoring enzyme activity.

Pharmacodynamic effects

Atropine is an effective and rapidly acting antidote to control the muscarinic symptoms of OP nerve agent intoxication produced by increased acetylcholine (ACh) levels and overstimulation of muscarinic receptors.

Atropine inhibits smooth muscle contraction and glands innervated by postganglionic cholinergic nerves. Peripheral effects include tachycardia, decreased production of saliva, sweat, bronchial, nasal, lachrymal and gastric secretions, decreased intestinal motility, and inhibition of micturition. Atropine increases sinus rate and sinoatrial and AV conduction. Usually heart rate is increased but there may be an initial bradycardia. Atropine inhibits secretions throughout the respiratory tract and relaxes bronchial smooth muscle producing bronchodilation. In the CNS, atropine has little effect, only partially counteracting the convulsive effects of OP poisoning. Atropine does not affect nicotinic receptors, and so does not treat the nicotinic signs and symptoms of OP poisoning that include muscle fasciculations, cramping, weakness and diaphragmatic failure.

Obidoxime is a causal antidote since it counteracts the cause of the symptoms induced by organophosphates (i.e., inhibition of acetylcholinesterase and subsequent accumulation of acetylcholine). It is an effective adjunct to the symptomatic and absolutely essential treatment of OP poisoning with Atropine. In addition, it is thought that Obidoxime elicits a complementary action to alleviate the nicotinic symptoms of nerve agent intoxication (such as those produced by ACh stimulation at the neuromuscular junction) that are not susceptible to treatment with atropine.

In summary, Atropine sulfate displaces ACh from the muscarinic receptors and Obidoxime chloride reactivates AChE. The combination of these substances with synergistic mechanisms

of action allows initial treatment in the field following exposure to potentially fatal OP nerve agents until the casualty reaches a Medical facility for further treatment.

Clinical Efficacy

For ethical reasons, there have been no clinical controlled studies carried out in humans testing the efficacy of Trobigard Auto-injector in subjects exposed to nerve agents. Two animal efficacy studies have been performed with Trobigard Auto-injector formulation, please see Section 5.3.

This medicinal product has been authorised under "exceptional circumstances". This means that for ethical reasons it has not been possible to obtain complete information on this medicinal product. The FAMHP will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption:

Atropine: Atropine is quickly absorbed after intramuscular administration. Maximum effects are achieved after 20-30 minutes.

Obidoxime: After intramuscular administration, maximum concentrations in the blood are reached after 20-40 minutes.

Distribution:

Atropine: After dosing, atropine distributes rapidly with only 5% remaining in the blood compartment. Volume of distribution is 1-1.7 L/kg. Initial distribution half-life is approximately one minute. The protein binding is 40-50%.

Atropine penetration is assumed to be greater into the central nervous system than into lumbar cerebrospinal fluid (CSF), compatible with the well-known central anticholinergic effects of the drug.

Obidoxime: Volume of distribution of obidoxime is 0.171 L/kg in healthy volunteers, 0.321 L/kg in patients with organophosphate intoxication. Obidoxime is not noticeably bound to plasma proteins.

Biotransformation:

Atropine: Atropine is metabolised in the liver by microsomal monooxygenases. The major metabolites of atropine include Noratropine (24%), atropine-N-oxide (equatorial isomer) (15%), tropine (2%) and tropic acid (3%) which are excreted in the urine. About 50% of the administered dose of atropine is excreted unchanged.

Obidoxime: No adequate studies on Obidoxime chloride biotransformation were conducted. Most of the administered dose of Obidoxime chloride is excreted unchanged in the urine.

Elimination:

Atropine: After dosing, atropine elimination fits a two-compartment model with an intrinsic clearance of 5.9-6.8 ml/kg/min. Biphasic elimination characterized a dominant plasma half-life of 2-3 hours in the elimination phase and terminal half-life of 12-38 hours. The biliary excretion of atropine is negligible.

Obidoxime: The half-life is approximately 2 hours. The elimination is renal, without liver metabolism. After 8 hours, 87% of the administered amount is excreted.

Linearity/non-linearity:

Atropine: The pharmacokinetics of atropine is nonlinear after intravenous administration of 0.5 to 4 mg.

Obidoxime: No data on dose-concentration of obidoxime chloride are available.

Characteristics in patients:

Differences in the pharmacokinetics of oximes, including obidoxime, have been observed in OP-poisoned patients in comparison to healthy volunteers. Specifically, half-life and mean plasma concentration are elevated in patients compared to healthy subjects due to a lower clearance. Changes in haemodynamics, a reduction in renal blood flow and potential renal insufficiency in OP-poisoned patients may account for these differences. These differences maybe of advantage in sustaining therapeutic levels and allowing a longer time period for reactivating OP inhibited AChE.

No such differences have been seen with atropine pharmacokinetics between OP-poisoned patients and healthy individuals.

5.3 Preclinical safety data

As it is unethical to carry-out clinical studies with Trobigard Auto-injector, two animal studies were carried out to establish the efficacy and safety of the product. One study determined the level of protection provided by human-equivalent doses of the Trobigard in guinea pigs subcutaneously (SC) exposed to (sub)lethal and supralethal levels of sarin (GB). The level of protection was defined by (1) the mitigation of signs and symptoms at a (sub)lethal GB dose and (2) increase of survival time at a supralethal GB dose. Pharmacokinetics of both Atropine sulfate and Obidoxime chloride were proportional at 1 and 3 human equivalent doses, and only a short, small increase in heart rate was observed as a side effect.

A second study was conducted to test the efficacy of Trobigard against VX poisoning in a guinea pig model and compare PK profiles of the Atropine sulfate and Obidoxime chloride components of Trobigard administered as coformulation and separately in both naïve and VX exposed animals. Trobigard-treated animals showed significant improvement in survival rate at both, sublethal and supralethal exposure levels of VX compared to vehicle-treated animals. Trobigard outperformed the single administration of atropine, and to a lesser extent obidoxime alone.

No animal studies to evaluate potential toxicity of the Atropine sulfate and Obidoxime chloride co-formulation have been conducted. Both atropine and obidoxime are drugs with a broad therapeutic range and relatively low self-toxicity.

Conducted animal studies demonstrated that Atropine levels reached the maximum concentration C_{max} faster after Trobigard Auto-injector formulation compared to injection with the single Atropine sulfate formulation. Other parameters representing bioavailability, C_{max} and AUC for Atropine sulfate, were the same. Obidoxime chloride PK were similar for Trobigard Auto-injector and single administration. Therefore, these results showed that combining the two drugs, Atropine sulfate and Obidoxime chloride, in an autoinjector

coformulation does not change behaviour of the drugs as compared to treatment and administration of the single components.

No evidence of drug to drug interaction between atropine and obidoxime in a co-formulation was found in the completed guinea pig studies conducted in support of this application. When PK profiles of atropine and obidoxime injected separately were compared to the Trobigard Auto-injector formulation administered to naïve animals, it was found that atropine reached the maximum concentration significantly faster in Trobigard Auto-injector formulation group. This finding shows no delay in reaching maximum concentration indicating that delay in atropinisation due to presence of obidoxime is not expected for Trobigard Auto-injector.

Atropine sulfate:

Safety pharmacology and Repeat dose toxicity:

Large doses of atropine produced repeated daily inhibition of glandular secretions in puppies; a lethal cachexia was similar to that of fibrocystic disease of the pancreas. However, Pancreatic fibrosis and cyst formation were not produced.

Acute toxicity:

Acute toxicity of atropine induced two types of deaths in rabbits; convulsive deaths that were produced in young rabbits within half an hour of the intramuscular injection of a lethal dose of atropine sulfate. In young male albino rats, intramuscular injection of lethal doses of atropine sulfate produced two types of death, an early hypothermic death and a delayed cachectic death. In dogs, Atropine produced mydriasis and bradycardia followed by transient increase in heart rate. Larger doses produced CNS depression, staggering gait, excitement, barking, tremor and convulsions particularly in hind legs, thirst and vomiting, depression, weakness and loss of appetite. Even larger doses paralyzed respiration and blocked spinal reflexes. Large repeat doses produced apathy, irritability, loss of appetite, vomiting and loss of weight.

Mutagenicity and Genotoxicity:

Atropine caused non-specific aggregation of chromosomes, considered to be of no cytogenetic danger. Atropine sulphate was assessed as negative in the Ames assay, using one or more Salmonella typhimurium standard strains (TA98, TA100, TA1535, TA1537 and TA1538).

Teratogenicity:

Atropine injection into chick eggs did not produce any teratogenic defects.

Atropine given to rat dams from days 7 to 19 of gestation resulted in avoidance learning deficits in their pups compared to controls. Findings suggested that prenatal exposure to sympatholytic drugs may produce adverse effects on the behavioural development of pups.

Reproductive toxicity:

Studies have shown atropine impaired fertility in male rats by inhibiting sperms and semen transportation from the vas deferens and seminal vesicle to the urethra during the process of emission.

Studies have shown that trace amounts of atropine appear in the breast milk and may cause antimuscarinic effects in the infant and that lactation may be inhibited

Obidoxime chloride:

According to animal studies obidoxime chloride is an active substance with relatively slight intrinsic toxicity and a large therapeutic index. The acute symptoms of poisoning are muscle weakness, states of motor paralysis and excitation, dyspnoea and respiratory paralysis.

Mutagenicity:

In vitro investigations with obidoxime chloride have not revealed any mutagenic properties.

In vivo mutagenicity data on Obidoxime chloride are not available.

Reproductive Toxicity:

There are no reprotoxicity studies in animals. In one case the administration of obidoxime (1250 mg in 24 hours) to a woman in the fifth month of pregnancy did not result in any adverse effects in the mother or the infant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenol
Water for Injections
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Storage Prior to Issuance to Individuals: Store below 25°C. Do not refrigerate or freeze.

In-use: From the date of delivery to the individual, the Trobigard Auto-injector can be used for a period of up to 3 months without any special storage conditions, except do not refrigerate or freeze. Product must then be discarded.

6.5 Nature and contents of container

The auto-injector is a fully integrated system consisting of a glass (Type I glass) cartridge containing 2 mL of solution for injection, needle, injection mechanism surrounded by a solid opaque housing and a red safety cap. It is for single-use, the cartridge is not replaceable. Each auto-injector is packaged in a plastic film.

The pack size is fifty (50) individual auto-injectors packaged in a cardboard carton.

6.6 Special precautions for disposal and other handling

A training device (without needle and active substance) is available to demonstrate the correct use of Trobigard Auto-injector. Training devices can be requested by emailing MedicalInformation@ebsi.com.

After the drug has been administered, the needle should be pushed against a hard surface to bend the needle back against the auto-injector. Keep used auto-injector(s) with the patient so other medical personnel will be aware of how many injections were administered.

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

7 MARKETING AUTHORISATION HOLDER

Emergent Netherlands B.V.
Strawinskylaan 411
1077XX
Amsterdam
The Netherlands

MedicalInformation@ebsi.com
Phone: +31 (0) 20 575 2727
Fax: +31 (0) 20 575 2726
24-hour (Belgium): 800.40719

8 MARKETING AUTHORISATION NUMBER(S)

BE580071

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}
Date of last renewal: {DD month YYYY}

10 DATE OF REVISION OF THE TEXT

01/2022