Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tisseel Kit 0.5 ml
Two-Component Fibrin Sealant

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1. Composition of TISSEEL, Sealer Protein Concentrate, Lyophilised

1 vial of TISSEEL of TISSEEL® KIT 1.0 ml, to be reconstituted with 1.0 ml of Aprotinin Solution 3000 KlU/ml. contains:

Active Ingredients:

Total Protein	100.00 – 130.00	mg
Clottable Protein	75.00 - 115.00	mg
thereof: Fibrinogen	70.00 - 110.00	mg
Plasmafibronectin (CIG)	2.00 - 9.00	mg
Factor XIII	10.00 - 50.00	U**
Plasminogen	0.04 - 0.12	mg

Excipients:

Human Albumin	10.00 - 20.00	mg
Glycine	15.00 - 35.00	mg
Sodium Chloride	2.00 – 4.00	mg
Sodium Citrate	4.00 - 8.00	mg
Triton WR 1339	0.20 - 0.40	mg

The vials of TISSEEL® KIT 0.5, 2.0, and 5.0 contain half, twice, and 5 times respectively the quantities indicated above.

** 1 unit of Factor XIII corresponds to the activity of this factor in 1 ml of fresh normal plasma.

2.2 Composition of Aprotinin Solution

Active Ingredients:

1 ml of the solution contains:

Aprotinin (bovine)	3000.00	KIU*

Excipients:

Water for Injections B.P. ad	1.00	ml

2.3 Composition of Human Thrombin, Lyophilised

1 vial contains 2, 4, 8 or 20 IU and 250, 500, 1000 or 2500 IU, respectively.

1 vial of Thrombin of TISSEEL® KIT 1.0, to be reconstituted with 1.0 ml of Calcium Chloride Solution, contains:

Active Ingredients:

Thrombin (human)		
	4.00	IU** or
	500.00	IU** respectively
Protein	50.00	mg

Excipients:

Soldium Chloride	10.00	mg
Glycine	3.00	mg

The vials of TISSEEL® KIT 0.5, 2.0, and 5.0 contain half, twice, and 5 times respectively the quantities indicated above.

* 880 Kallidogenase Inactivator Units (KIU) correspond to I European Pharmacopoeia Unit (EPU)

** 1 International Unit (1.U.) of Human Thrombin is defined as the activity contained in 0.0853mg of the 1st International Standard for Human Thrombin

2.4 Composition of Calcium Chloride Solution

1 ml of the solution contains:

Active Ingredients:

Calcium Chloride	4.44	(40 μmol)

Excipients:

Water for Injections B.P. ad	1.00	ml

3 PHARMACEUTICAL FORM

- 1 vial containing the lyophilised and vapour heated protein sealant TISSEEL (of human origin)*, which is to be dissolved in aprotinin solution;
- 1 vial containing aprotinin solution (bovine) at a concentration of 3,000 KIU**/ml;
- 2 vials containing lyophilised thrombin (human) for preparing a thrombin / calcium chloride solution at either of the following concentrations:
- 5001.U. ***/ml
- 41. U. ***/ml;
- 1 vial containing calcium chloride solution 40mmol/l

Route of administration: Topical administration only.

TISSEEL KIT is available in presentations of 0.5ml, 1.0mI, 2.0ml, and 5.0ml, with each pack including products, syringes, and needles for reconstitution and application.

* The vial contains a magnetic spin propeller for facilitating the dissolution process by using FIBRINOTHERM.
** 880 Kallidogenase Inactivator Units (K.I.U.) correspond to I European Pharmacopoeia Unit (EPU)
*** 1 International Unit (1. U.) of Human Thrombin is defined as the activity contained in 0.0853mg of the 1st International Standard for Human Thrombin

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As a coagulant for use as a tissue sealant and haemostatic, for surgical incisions, plastic surgical repairs, orthopaedic, traumatic, and dental surgery.

4.2 Posology and method of administration

The required dose of TISSEEL Solution depends on the size of the surface to be sealed or coated or on the size of the defect to be packed.

Maximum size of the area to be sealed	**Required pack sizes of TISSEEL KIT**
4 cm^2	TISSEEL KIT 0.5
8 cm^2	TISSEEL KIT 1.0
16cm^2	TISSEEL KIT 2.0
40cm^2	TISSEEL KIT 5.0

This is applied topically to the site. The dose is also dependent on the application method. With spraying, TISSEEL KIT 1.0 will be sufficient to coat an area of 25-100 cm^2 depending on the specific indication and the individual case.

It is desirable for the TISSEEL Sealant to be absorbed slowly during the wound healing process. For that reason, Aprotinin Solution is used for reconstitution of the freeze-dried TISSEEL, Sealer Protein Concentrate. The concentration of the Aprotinin Solution supplied with the Kit may be varied to control the rate at which the sealant will be absorbed. If the Aprotinin Solution is diluted with Sterile Water for Injections, the sealant will be absorbed faster. This may also be desirable if a recipient surface is known to have a low fibrinolytic activity of its own.

The setting rate of the sealant, on the other hand, depends on the concentration of the Thrombin Solution used. While the sealant may take up to one minute to set with a Thrombin concentration of 4 i.u./ml, this setting process will be complete within seconds if the higher Thrombin concentration of 500 i.u./ml is used. The higher Thrombin concentration may be advantageous to achieve haemostasis, while the lower Thrombin concentration is better suited to seal tissue because it allows time for approximation of the wound areas.

4.3 Contraindications

TISSEEL Kit alone is not indicated for the treatment of massive and brisk arterial or venous bleeding.

Known hypersensitivity to aprotinin (or other bovine proteins) or known hypersensitivity to any other components of TISSEEL Kit.

Injection into the nasal mucosa must be avoided, as severe allergic-anaphylactiod reactions have been observed and thromboembolic complications may occur in the area of the ophthalmic artery.

4.4 Special warnings and precautions for use

Special Warnings
TISSEEL Solution and Thrombin Solution are made from human plasma. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses or other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV, and for the non-enveloped virus HAV.

The measures taken may be of limited value against small non-enveloped viruses such as parvovirus B19.

Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g., hemoltic anemia).

It is strongly recommended that every time a patient receives a dose of TISSEEL Kit, the name and batch number of the product are recorded in order to maintain a record of the batches used.

Precautions
Injection of Tisseel and/or Thrombin solution/s carries the risk of an anaphtylactiod reaction. Intravascular and intraventricular administration carries the additional risk of a thromboembolic complication. Both complications may be life-threatening. Therefore, Tisseel and/or Thrombin solutions/s should be applied topically only.

Injection into the nasal mucosa must be avoided, as severe allergic-anaphylactiod reactions have been observed and thromboembolic complications may occur in the area of the ophthalmic artery.

The spraying of fibrin sealant may be carried out only under visual control by using the Tissomat, **the minimum spraying distance being 10cm.** Consequently, the Duploject system with Spray Head must not be used in enclosed body areas. The user is cautioned against the spray application of Tisseel with devices provided by other manufacturers.

Hypersensitivity against bovine proteins or repeated application of TISSEEL KIT may in very rare cases lead to allergic or anaphylactic reactions. If the symptoms require any treatment this should be done in the usual way, e.g. with antihistamines, corticoids, adrenalines.

* All plasma units used for manufacture are ALT tested and non-reactive in tests for HBs-antigen and antibodies to HCV, HIV-1 and HIV-2. Before further processing all individual plasma donations are subjected to an inventory hold of at least three months for a possible look-back of plasma donations suspected of infection.

** IQ-PCR = IMMUNO Quality-Assured Polymerasc Chain Reaction.

Fibrin sealant is sprayed using pressurised gas. Any application of pressurised gas may be associated with the risk of air embolism, gas emphysema, or tissue or organ rupture, which may be life-threatening.

Concomitant local administration of antibiotics may interfere with the coagulant capacity of this preparation. Early lysis of the clot may occur in the presence of local infection. Neither of the two components, separately or combined, must be administered by the intravascular route. As TISSEEL and Thrombin Solutions can be denatured by contact with alcohol, iodine or other antiseptics any such substances should be removed before applying the sealant components.

If possible cover all tissue adjacent to the site of sealing before applying TISSEEL and Thrombin Solutions.

All syringes, needles and containers used in the preparation of the product must be discarded after use using appropriate precautions.

4.5 Interaction with other medicinal products and other forms of interaction

None known. The sealant can even be applied in fully heparinised patients (e.g. extracorporeal circulation).

4.6 Pregnancy and lactation

No undesired side effects are known during pregnancy or lactation.

According to generally recognized recommendations, medicinal products should be given during pregnancy or lactation only when strictly indicated.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

TISSEEL Kit should not be applied intravenously, since this may lead to anaphylactic reactions and/or thromboembolic complications, which both may be life-threatening. Especially in coronary bypass surgery, TISSEEL Kit should be applied with caution to minimize any risk of intravascular application.

4.9 Overdose

Not applicable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Fibrin sealing corresponds to the last step of blood coagulation and is based on the transformation of fibrinogen into fibrin. The fibrinogen molecule consists of 6 polypeptide chains. The 3 polypeptide chains - alpha, beta, and gamma - are symmetrically arranged (in pairs) in the two halves of the molecule. By the action of thrombin, fibrinopeptides A and B are split off, thus transforming fibrinogen into fibrin monomers. By end-to-end and side-to-side aggregation, these monomers become fibrin polymer.

In the presence of $CaCI_2$, this polymer is transformed by the action of Factor XIII previously activated by thrombin into fibrin which is insoluble in urea. Between the alpha and gamma chains of the fibrin monomers covalent bridges are formed. The fibrin thus produced adheres physically and chemically to the tissues to be sealed and has particular affinity to collagen fibres. As wound healing sets in, fibroblasts and capillaries proliferate into the wound area along the matrix provided by the fibrin network.

This process depends on many factors, and thrombin, fibrin, and Factor XIII have a positive influence on the proliferation of the fibroblasts. The process of wound healing is followed by the proteolytic and phagocytic degradation of the fibrin network. Fibrinolysis depends, among others, on plasminogen activators contained in the respective tissue at different concentrations. The last stage is the substitution of the fibrin layer by connective tissue and the formation of the final scar tissue

5.2 Pharmacokinetic properties

As a biologic material, Tisseel becomes completely absorbed at a rate which depends both on the fibrinolytic activity of the surrounding tissue and the quantity of fibrinolysis inhibitor added. In the course of wound healing Tisseel is gradually replaced by ingrowing tissue, thrombin is inactivated by the physiological protease inhibitors, calcium chloride is subjected to the calcium and chloride catabolisms of the organism, and aprotinin and its metabolites are eliminated by the kidney.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

6.1.1 Excipients of TISSEEL, Sealer Protein Concentrate, Lyophilised

Human Albumin	complying with Ph.Eur.
Glycine	complying with Ph.Eur.
Sodium Chloride	complying with Ph.Eur.
Sodium Citrate	
Triton WR 1339	complying with USP

6.1.2. Excipients of the Aprotinin Solution

Water for Injections complying with Ph.Eur

6.1.3. Excipients of Human Thrombin, Lyophilised

Sodium Chloride	complying with Ph.Eur
Glycine	complying with Ph.Eur

6.1.4. Excipients of the Calcium Chloride Solution

Water for Injections	complying with Ph.Eur

6.2 Incompatibilities

As the TISSEEL and Thrombin solutions can be denatured following contact with solutions containing alcohol, iodine or heavy metals (contained e.g. in disinfectants), any such substances should be removed before applying the sealant.

6.3 Shelf Life

TISSEEL® KIT has a shelf life of 2 years from the date of manufacture when stored between +2°C and +8°C.

Do not use after the expiry date indicated on the container and package labels.

Reconstituted TISSEEL and Thrombin solutions must be used within 4 hours.

6.4 Special precautions for storage

TISSEEL® KIT must be stored between +2°C and +8°C.

6.5 Nature and contents of container

TISSEEL® KIT 0.5
For 0.5 ml of reconstituted TISSEEL® Solution **and** 0.5 ml Thrombin Solution

TISSEEL® KIT 1.0
For 1.0 ml of reconstituted TISSEEL® Solution **and** 1.0 ml Thrombin Solution

TISSEEL® KIT 2.0
For 2.0 ml of reconstituted TISSEEL® Solution **and** 2.0 ml Thrombin Solution

TISSEEL® KIT 5.0
For 5.0 ml of reconstituted TISSEEL® Solution **and** 5.0 ml Thrombin Solution

Each presentation ofTISSEEL® KIT contains the following products:

- 1 vial containing lyophilised TISSEEL, Sealer Protein Concentrate;
- 1 vial containing lyophilised Human Thrombin 4 I.U./ml;
- 1 vial containing lyophilised Human Thrombin 500 I.U./ml;
- 1 vial containing Aprotinin Solution;
- 1 vial containing Calcium Chloride Solution;
- 1 kit for reconstitution and application (syringes, needles and DUPLOJECT Application System).

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

1. How to Prepare TISSEEL Solution

Freeze-dried TISSEEL is reconstituted in the Aprotinin Solution of 3,000 KlU/ml. To obtain lower concentrations, dilute the solution with Sterile Water for Injections.

Note: For fascicular nerve sealing, use an Aprotinin concentration of 100 KlU/ml. To obtain this concentration, dilute 0.1 ml (0.2 ml if TISSEEL KIT 5.0 is used) with 3 ml (5 ml) of Sterile Water for Injections using the blue-scaled syringe.

Reconstitution of Freeze-Dried TISSEEL Using FIBRINOTHERM™
For ease of handling, a combined heating and stirring device, FIBRINOTHERM, has been developed to meet the specific requirements of reconstituting freeze-dried TISSEEL. The FIBRINOTHERM is a thermo-block with a magnetic stirrer (the bottles for freeze-dried TISSEEL are equipped with stainless steel bars to stir the contents). Heating and stirring can be operated independently. In a first step, FIBRINOTHERM heats up to 37°C and then maintains that temperature constantly with minimum variation. The FIBRINOTHERM has been designed to hold the various bottle sizes of freeze-dried TISSEEL and Aprotinin Solution.

- Place the bottles containing freeze-dried TISSEEL and Aprotinin Solution into the appropriate openings of FIBRINOTHERM and operate the orange switch. Wait until the signal lamp goes out; the FIBRINOTHERM has now reached 37°C. Preheat the bottles for ten minutes.
- Transfer the Aprotinin Solution into the bottle containing freeze-dried TISSEEL using a blue-scaled syringe of appropriate size (or syringe that has been used for dilution of Aprotinin Solution).
- Place the bottle into the largest opening of the FIBRINOTHERM (if necessary, use adapters). Turn on the stirrer with the green switch and stir the contents for 8-10 minutes.
- Reconstitution of freeze-dried TISSEEL is complete as soon as no undissolved particles are detectable. Otherwise, replace it into the FIBRINOTHERM and stir for a few minutes more until the solution appears homogeneous.

Note: If not used immediately, keep the TISSEEL Solution at 37°C without stirring. To ensure homogeneity switch on the stirrer shortly before drawing up the solution.

Reconstitution of Freeze-Dried TISSEEL Using a Water-Bath:
- Preheat the bottle with freeze-dried TISSEEL and the bottle with the Aprotinin Solution to about 37°C (but not beyond 40°C).
- Transfer the Aprotinin Solution into the bottle containing freeze-dried TISSEEL using a blue-scaled syringe of appropriate size (or syringe that has been used for dilution of Aprotinin Solution).
- Allow the bottle to stand at 37°C for one minute.
- Swirl briefly and vigorously with a circular motion (avoid excessive frothing) and replace the bottle into the water-bath for another 10-15 minutes.
- Reconstitution of freeze-dried TISSEEL is complete as soon as no undissolved particles are detectable. Otherwise, swirl again briefly and keep the bottle at 37°C for a few minutes more.

Note: If not used immediately, keep the TISSEEL Solution at 37°C. To ensure homogeneity, swirl with a circular motion (avoiding frothing) before drawing up the solution.

2. How to Prepare Thrombin Solution

Depending on the desired Thrombin concentration, either transfer the contents of the bottle of Calcium Chloride Solution into the bottle containing freeze-dried Thrombin 500 (quick solidification) or Thrombin 4 (slow solidification).

Use one of sterile black-scaled syringes for preparing Thrombin Solution.

Swirl briefly. Keep the Thrombin Solution at 37°C until used. Draw up an amount of Thrombin Solution equal to the amount of TISSEEL Solution that will be used into a sterile black-scaled syringe using aseptic precautions.

Note: To avoid premature setting, do not use the syringes and needles previously used for reconstitution of freeze-dried TISSEEL.

3. Application

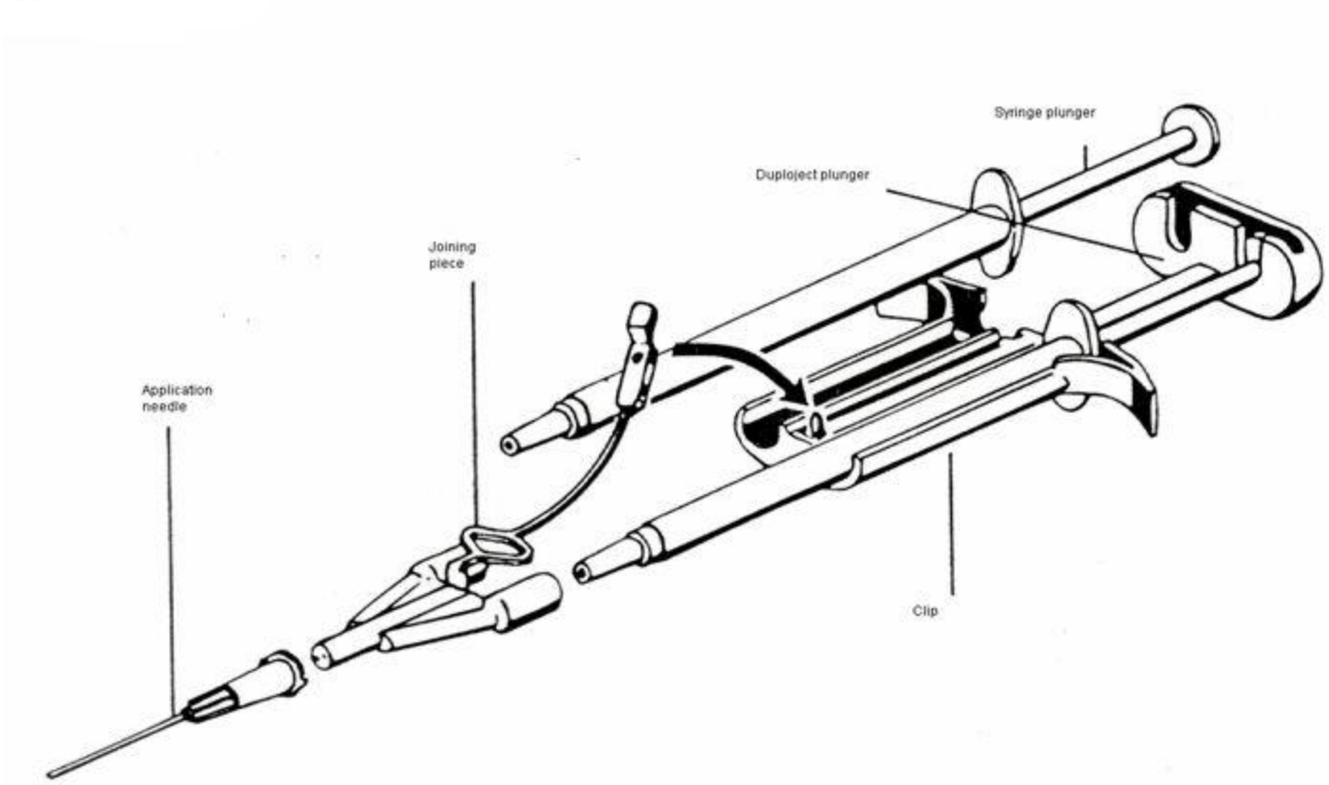
The syringes and needles used for administration must be separate from those used for reconstitution.

4. Simultaneous Application Using DUPLOJECT™-System:

The DUPLOJECT-System allows simultaneous application of the two components and ensures that they are quickly and thoroughly mixed, which is essential for the sealant to gain optimum strength. Either Thrombin concentration can be used.

a) Simultaneous Application Using DUPLOJECT and Application Needle:

The sterile DUPLOJECT-System consists of a clip for two identical disposable syringes and a common plunger which ensures that equal volumes of the two components are fed over a common joining piece before being mixed in the application needle and ejected.



Operating Instructions:

- Place the syringes filled with TISSEEL and Thrombin Solutions into the clip. Both syringes should be filled with equal amounts and should not contain any air bubbles.
- Connect the nozzles of the two syringes with the joining pieces. Ensure a firm attachment. Secure the joining piece by fastening the strap to the clip.
- Fit an application needle onto the joining piece. Do not remove the remaining air from inside the joining piece or application needle as the apertures of the needle may clog before application of the sealant.
- Apply the sealant onto the recipient surface or surfaces if two parts of tissue need to be glued together.

Note: Only the syringes contained in the Kit for Reconstitution and Application are designed to fit perfectly into the DUPLOJECT clip. Any other syringe may cause problems since exact and firm adaptation to the joining piece cannot be guaranteed. If the procedure of applying the two components with DUPLOJECT is interrupted, replace the application needle by a new one when sealing is resumed (three spare needles come with the Kit). Only replace the application needle immediately prior to resuming sealing. Otherwise, the apertures of the joining piece will clog, which will then also require replacing (one spare joining piece comes with the Kit).

b) Simultaneous Application Using DUPLOJECT and Spray Set

This method of application is particularly suitable for spraying larger areas, e.g. in skin grafting or to control oozing.

DUPLOJECT is used for the sealant application, together with a specially designed spray head which is fitted to the nozzles of the syringes. The two components can then be sprayed simultaneously using sterile propellent gas (compressed air, nitrogen or C02; pressure: approx. 2-3 bar, 5-10 l/min.). The volume of the solutions ejected is controlled by the DUPLOJECT plunger. Spray at a distance of at least 10-20 cm.

Connection for sterile propellent gas
Note: A detailed description including precautions for use is enclosed with each pack of spray sets.

c) Simultaneous Application Using DUPLOJECT and Application Catheter.
This method of application is particularly suitable for operating sites where access is difficult or for use in endoscopy or minimal invasive surgery.

Note: A detailed description including precautions for use is enclosed with each pack of application catheters.

d) Simultaneous Application by Premixing
Mix equal volumes of the two components and immediately apply them to the recipient surface or surfaces. When the low Thrombin concentration of 4 i.u./ml is used, approximately one minute is available for mixing the components, applying the sealant, and approximating the wound areas. If desired, the sealant can be mixed with spongiosa to pack bone defects.

Consecutive Application
Apply the two components in two layers. Apply TISSEEL Solution to the recipient surface or surfaces first, then top with an equal amount of Thrombin Solution. Alternatively, when two parts are to be glued, apply one component to one surface, the other component to the opposite surface.

Note: To prevent the sealant from adhering to gloves and instruments, wet these with saline before contact with the sealant.

5. Gluing of Tissue
After the two components have been applied, approximate the wound areas fix or hold the glued parts in the desired position for three to five minutes to ensure that the setting sealant adheres firmly to the surrounding tissue. The solidified sealant reaches its ultimate strength after about two hours (70% after about ten minutes).

Note: In order to avoid excess formation of granulation tissue and slow absorption of the sealant, only apply thin layers of the two components.

7 MARKETING AUTHORISATION HOLDER

Baxter Healthcare,
Caxton Way,
Thetford,
Norfolk,
IP24 3SE,
UK

8 MARKETING AUTHORISATION NUMBER

PA 0167/129/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 August 1983

Date of last renewal: 05 August 2003

10 DATE OF REVISION OF THE TEXT

March 2007