SUMMARY OF PRODUCT CHARACTERISTICS

1 TRADE NAME OF THE MEDICINAL PRODUCT

Technescan MAG3
(Mallinckrodt Medical catalogue number: DRN 4334

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains:
Betiatide 1 mg

To be used with sodium pertechnetate (^{99m}Tc) for the preparation of the diagnostic agent: Technetium (^{99m}Tc) tiatide.

3 PHARMACEUTICAL FORM

Powder for solution for injection. ATC code: VO9 A03

4 CLINICAL PARTICULARS

4.1 Indications

After reconstitution and labelling with sodium pertechnetate (^{99m}Tc) solution the diagnostic agent technetium (^{99m}Tc) tiatide may be used for the evaluation of nephrological and urological disorders in particular for the study of morphology, perfusion, function of the kidney and characterisation of urinary outflow.

4.2 Posology and method of administration

Adults and the elderly : 37-185 MBq (1-5 mCi), depending on the pathology to be studied and the method to be used. Studies of renal blood flow or transport through the ureters generally require a larger dose than studies of intra-renal transport, whereas renography requires smaller activities than sequential scintigraphy.

Children:
Although Technescan MAG3 may be used in paediatric patients, formal studies have not been performed. Clinical experience indicates that for paediatric use the activity should be reduced. Because of the variable relationship between the size and body weight of patients it is sometimes more satisfactory to adjust activities to body surface area. A practical approach is to adopt the recommendations of the Paediatric Task Group of the European Association of Nuclear Medicine (EANM). See table below.

Activities in children. Fraction of adult activity (Paediatric Task Group EANM, 1990).		
3 kg = 0.1	22 kg = 0.50	42 kg = 0.78
4 kg = 0.14	24 kg = 0.53	44 kg = 0.80
6 kg = 0.19	26 kg = 0.56	46 kg = 0.82
8 kg = 0.23	28 kg = 0.58	48 kg = 0.85
10 kg = 0.27	30 kg = 0.62	50 kg = 0.88
12 kg = 0.32	32 kg = 0.65	52-54 kg = 0.90
14 kg = 0.36	34 kg = 0.68	56-58 kg = 0.92
16 kg = 0.40	36 kg = 0.71	60-62 kg = 0.96
18 kg = 0.44	38 kg = 0.73	64-66 kg = 0.98
20 kg = 0.46	40 kg =0.76	68 kg = 0.99

Reduction of the amount of radioactivity to less than 10% of the dose for adults will generally result in technically unsatisfactory procedures. In general, the risks are likely to relate to the level of radiation, as the chemical doses are quite small (about 0.2 mg for 185 MBq).

The administration of a diuretic or an ACE inhibitor during the diagnostic procedure is sometimes used for differential diagnosis of nephrological and urological disorders. The scintigraphic investigation is usually performed immediately after administration.

4.3 Contraindications

None.

4.4 Special warnings and special precautions for use

4.4.1 The patient should be well hydrated before the start of the examination and urged to void as often as possible during the first hours after the study in order to reduce radiation.

4.4.2 Radiopharmaceutical agents should only be used by qualified personnel with the appropriate government authorization for the use and manipulation of radionuclides.

4.4.3 This radiopharmaceutical may be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the local competent official organisations.

4.4.4 Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken, complying with the requirements of Good Manufacturing Practice for pharmaceuticals.

4.4.5 The agent is not suited for exact monitoring of effective renal plasma flow respectively blood flow in patients with seriously impaired renal function.

4.4.6 Small amounts of ^{99m}Tc-labelled impurities may be present and/or are formed during the labelling process. As some of these impurities are

distributed to the liver and excreted via the gall bladder they may influence the late phase (after 30 minutes) of a dynamic renal study due to the overlap of kidney and liver in the region of interest.

4.5 Interaction with other medicaments and other forms of interaction

Technetium (^{99m}Tc) tiatide has not been described to interfere with agents commonly prescribed to given to patients requiring the above mentioned investigations (e.g. antihypertensives and medicinal agents used to treat or prevent organ transplant rejection). However, the single administration of a diuretic or ACE inhibitor is sometimes used in the differential diagnosis of nephrological and urological disorders. Administered contrast media may impair tubular renal excretion and thereby influence the technetium (^{99m}Tc) tiatide clearance.

4.6 Pregnancy and lactation

When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainty exists it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques which do not involve ionising radiation should be considered.

Radionuclide procedures carried out on pregnant women also involve radiation doses to the fetus. Only imperative investigations should be carried out during pregnancy, when likely benefit exceeds the risks incurred by mother and fetus.

Before administering a radioactive medicinal product to a mother who is breast-feeding consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast-feeding and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of activity in breast milk. If administration above 100 MBq is considered necessary, the mother should be advised to interrupt breastfeeding until measurements on the expressed milk samples indicate that the effective dose to the infant will be less than 1 mSv. Interruption of breastfeeding is not necessary if activities below 100 MBq are administered. The expressed feeds should be discarded. In the event of uncertainty it is usually advised that breast-feeding can be restarted when the level in the milk will not result in a radiation dose to a child greater than 1 mSv.

4.7 Effects on the ability to drive and use machines

Have not been described.

4.8 Undesirable effects

A few mild anaphylactoid reactions have been reported, characterised by urticarial rash, swelling of eyelids and coughing. Although the probability of the occurrence of such reactions is small, the appropriate treatment of allergic reactions (adrenaline, corticosteroids and antihistamines) should always be kept available for immediate use. Occasionally vasovagal

reactions of a mild nature have been reported.

3A cerebral convulsion in a sedated fifteen days old child has been reported, but causative relation with the administration of Technescan MAG3 was not established.

For each patient, exposure to ionising radiation must be justifiable on the basis of likely benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic. Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations the current evidence suggests that these adverse effects will occur with low frequency because of the low radiation doses incurred. For most diagnostic investigations using nuclear medicine procedures the radiation dose delivered (Effective Dose Equivalent) is less than 20 mSv. Higher doses might be justified in some clinical circumstances.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medical 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 listed in Appendix V*.

4.9 Overdose

The risk of an excessive technetium (^{99m}Tc) tiatide dose is largely theoretical and most likely to be due to excessive radiation exposure. In such circumstances the radiation to the body (kidney, bladder and gall bladder) can be reduced by forced diuresis and frequent bladder voiding.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

At the chemical doses envisaged technetium (^{99m}Tc) tiatide Injection has no known pharmacodynamic action.

Measuring the activity over the kidneys allows renal blood flow, intrarenal tubular transit times and excretion via the outflow tracts to be recorded separately for both kidneys.

5.2 Pharmacokinetic properties

After intravenous injection technetium (^{99m}Tc) tiatide is rapidly cleared from the blood by the kidneys.

Technetium (^{99m}Tc) tiatide has a relatively high binding to plasma proteins. In normal renal function 70% of the administered dose has been excreted after 30 min. and more than 95% after 3 hours. These latter percentages are dependent on the pathology of the kidneys and the urogenital system. The mechanism of excretion is predominantly based on tubular secretion. Glomerular filtration accounts for 11% of total clearance.

5.3 Preclinical safety data

Acute, subacute (8 days) and chronic (13 weeks) toxicity studies as well as mutagenicity studies were performed. At the studied dose levels, up to 1000 times the maximal human dose, no toxicological effects were observed. Similarly, mutagenic effects have not been observed.

5.4 Radiation dosimetry

5.4.1. Absorbed doses: ^{99m}Tc MAG3 (Normal renal function)

^{99m}Tc 6.02 h

	Absorbed dose per unit activity administered (mGq/MBq)				
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	3.9E-04	5.1E-04	8.2E-04	1.2E-03	2.5E-03
Bladder	1.1E-01	1.4E-01	1.7E-01	1.8E-01	3.2E-01
Bone surfaces	1.3E-03	1.6E-03	2.1E-03	2.4E-03	4.3E-03
Brain	1.0E-04	1.3E-04	2.2E-04	3.5E-04	6.1E-04
Breast	1.0E-04	1.4E-04	2.4E-04	3.9E-04	8.2E-04
Gall bladder	5.7E-04	8.7E-04	2.0E-03	1.7E-03	2.8E-03
GI-tract					
Stomach	3.9E-04	4.9E-04	9.7E-04	1.3E-03	2.5E-03
SI	2.3E-03	3.0E-03	4.2E-03	4.6E-03	7.8E-03
Colon	3.4E-03	4.3E-03	5.9E-03	6.0E-03	9.8E-03
(ULI	1.7E-03	2.3E-03	3.4E-03	4.0E-03	6.7E-03)
(LLI	5.7E-03	7.0E-03	9.2E-03	8.7E-03	1.4E-02)
Heart	1.8E-04	2.4E-04	3.7E-04	5.7E-04	1.2E-03
Kidneys	3.4E-03	4.2E-03	5.9E-03	8.4E-03	1.5E-02
Liver	3.1E-04	4.3E-04	7.5E-04	1.1E-03	2.1E-03
Lungs	1.5E-04	2.1E-04	3.3E-04	5.0E-04	1.0E-03
Muscles	1.4E-03	1.7E-03	2.2E-03	2.4E-03	4.1E-03
Oesophagus	1.3E-04	1.8E-04	2.8E-04	4.4E-04	8.2E-04
Ovaries	5.4E-03	6.9E-03	8.7E-03	8.7E-03	1.4E-02
Pancreas	4.0E-04	5.0E-04	9.3E-04	1.3E-03	2.5E-03
Red marrow	9.3E-04	1.2E-03	1.6E-03	1.5E-03	2.1E-03
Skin	4.6E-04	5.7E-04	8.3E-04	9.7E-04	1.8E-03
Spleen	3.6E-04	4.9E-04	7.9E-04	1.2E-03	2.3E-03
Testes	3.7E-03	5.3E-03	8.1E-03	8.7E-03	1.6E-02
Thymus	1.3E-04	1.8E-04	2.8E-04	4.4E-04	8.2E-04
Thyroid	1.3E-04	1.6E-04	2.7E-04	4.4E-04	8.2E-04
Uterus	1.2E-02	1.4E-02	1.9E-02	1.9E-02	3.1E-02
Remaining Organs	1.3E-03	1.6E-03	2.1E-03	2.2E-03	3.6E-03
Effective dose (mSv/MBq)	7.0E-03	9.0E-03	1.2E-02	1.2E-02	2.2E-02
Bladder wall contributes up to 80% of the effective dose.					
Effective dose if bladder is emptied 1 or 0,5 hours after administration:					
1 hour	2.5E-03	3.1E-03	4.5E-03	6.4E-03	6.4E-03
30 min	1.7E-03	2.1E-03	2.9E-03	3.9E-03	6.8E-03

5.4.2. Absorbed doses: ^{99m}Tc MAG3 (Abnormal renal function)

^{99m}Tc 6.02 h

	Absorbed dose per unit activity administered (mGq/MBq)				
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	1.6E-03	2.1E-03	3.2E-03	4.8E-03	8.6E-03
Bladder	8.3E-02	1.1E-01	1.3E-01	1.3E-01	2.3E-01
Bone surfaces	2.2E-03	2.7E-03	3.8E-03	5.0E-03	9.1E-03
Brain	6.1E-04	7.7E-04	1.3E-03	2.0E-03	3.6E-03
Breast	5.4E-04	7.0E-04	1.1E-03	1.7E-03	3.2E-03
Gall bladder	1.6E-03	2.2E-03	3.8E-03	4.6E-03	6.4E-03
GI-tract					
Stomach	1.2E-03	1.5E-03	2.6E-03	3.5E-03	6.1E-03
SI	2.7E-03	3.5E-03	5.0E-03	6.0E-03	1.0E-02
Colon	3.5E-03	4.4E-03	6.1E-03	6.9E-03	1.1E-02
(ULI	2.2E-03	3.0E-03	4.3E-03	5.6E-03	9.3E-03)
(LLI	5.1E-03	6.3E-03	8.5E-03	8.6E-03	1.4E-02)
Heart	9.1E-04	1.2E-03	1.8E-03	2.7E-03	4.8E-03
Kidneys	1.4E-02	1.7E-02	2.4E-02	3.4E-02	5.9E-02
Liver	1.4E-03	1.8E-03	2.7E-03	3.8E-03	6.6E-03
Lungs	7.9E-04	1.1E-03	1.6E-03	2.4E-03	4.5E-03
Muscles	1.7E-03	2.1E-03	2.9E-03	3.6E-03	6.4E-03
Oesophagus	7.4E-04	9.7E-04	1.5E-03	2.3E-03	4.1E-03
Ovaries	4.9E-03	6.3E-03	8.1E-03	8.7E-03	1.4E-02
Pancreas	1.5E-03	1.9E-03	2.9E-03	4.3E-03	7.4E-03
Red marrow	1.5E-03	1.9E-03	2.6E-03	3.1E-03	5.0E-03
Skin	7.8E-04	9.6E-04	1.5E-03	2.0E-03	3.8E-03
Spleen	1.5E-03	1.9E-03	2.9E-03	4.3E-03	7.4E-03
Testes	3.4E-03	4.7E-03	7.1E-03	7.8E-03	1.4E-02
Thymus	7.4E-04	9.7E-04	1.5E-03	2.3E-03	4.1E-03
Thyroid	7.3E-04	9.5E-04	1.5E-03	2.4E-03	4.4E-03
Uterus	1.0E-02	1.2E-02	1.6E-02	1.6E-02	2.7E-02
Remaining Organs	1.7E-03	2.1E-03	2.8E-03	3.4E-03	6.0E-03
Effective dose (mSv/MBq)	6.1E-03	7.8E-03	1.0E-02	1.1E-02	1.9E-02

5.4.3. Absorbed doses: ^{99m}Tc MAG3 (Acute unilateral renal function)

^{99m}Tc 6.02 h

	Absorbed dose per unit activity administered (mGq/MBq)				
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	1.1E-02	1.4E-02	2.2E-02	3.2E-02	5.5E-02
Bladder	5.6E-02	7.1E-02	9.1E-02	9.3E-02	1.7E-01
Bone surfaces	3.1E 03	4.0E-03	5.8E-03	8.4E-03	1.7E-02
Brain	1.1E-04	1.4E-04	2.3E-04	3.9E-04	7.5E-04
Breast	3.8E-04	5.1E-04	1.0E-03	1.6E-03	3.0E-03
Gall bladder	6.2E-03	7.3E-03	1.0E-02	1.6E-02	2.3E-02
GI-tract					
Stomach	3.9E-03	4.4E-03	7.0E-03	9.3E-03	1.2E-02
SI	4.3E-03	5.5E-03	8.5E-03	1.2E-02	1.9E-02
Colon	3.9E-03	5.0E-03	7.2E-03	9.2E-03	1.5E-03
(ULI	4.0E-03	5.1E-03	7.6E-03	1.0E-02	1.6E-02)
(LLI	3.8E-03	4.8E-03	6.7E-03	8.2E-03	1.3E-02)
Heart	1.3E-03	1.6E-03	2.7E-03	4.0E-03	6.1E-03
Kidneys	2.0E-01	2.4E-01	3.3E-01	4.7E-01	8.1E-01
Liver	4.4E-03	5.4E-03	8.1E-03	1.1E-02	1.7E-02
Lungs	1.1E-03	1.6E-03	2.5E-03	3.9E-03	7.2E-03
Muscles	2.2E-03	2.7E-03	3.7E-03	5.1E-03	8.9E-03
Oesophagus	3.8E-04	5.4E-04	8.5E-04	1.5E-03	2.3E-03
Ovaries	3.8E-03	5.1E-03	7.1E-03	9.2E-03	1.5E-02
Pancreas	7.4E-03	9.0E-03	1.3E-02	1.8E-02	2.9E-02
Red marrow	3.0E-03	3.6E-03	5.0E-03	6.0E-03	8.3E-03
Skin	8.2E-04	1.0E-03	1.5E-03	2.2E-03	4.2E-03
Spleen	9.8E-03	1.2E-02	1.8E-02	2.6E-02	4.0E-02
Testes	2.0E-03	2.9E-03	4.5E-03	5.0E-03	9.8E-03
Thymus	3.8E-04	5.4E-04	8.5E-04	1.5E-03	2.3E-03
Thyroid	1.7E-04	2.3E-04	4.5E-04	9.2E-04	1.6E-03
Uterus	7.2E-03	8.7E-03	1.2E-02	1.3E-02	2.2E-02
Remaining Organs	2.1E-03	2.6E-03	3.6E-03	4.7E-03	8.0E-03
Effective dose (mSv/MBq)	1.0E-02	1.2E-02	1.7E-02	2.2E-02	3.8E-02

The effective dose equivalent after a dose of 185 MBq for a 70 kg individual would be 2.0 mSv when the bladder is voided 2 hours after administration.

Although no comparative dosimetric studies have been performed in patients, it is anticipated that the EDE will be lower in patients with renal insufficiency/failure than those with normal renal function. This relates to the contribution of urinary bladder to overall tissue exposure.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium tartratedihydrate

Tin(II)chloride dihydrate

Hydrochloric acid

After reconstitution of the vial contents and after labelling with the eluate of a ^{99m}Tc-generator (usually 0.9% sodium chloride) the aqueous injection solution will in addition to sodium chloride also contain disodium tartrate and tin(II) chloride. The vial does not contain a preservative agent.

Properties of the medicinal product after labelling:
Clear to slightly opalescent, colourless, aqueous solution.
pH : 5.0-6.0
Osmolality : slightly hypertonic.

6.2 Incompatibilities

Major incompatibilities: not known. However, in order not to compromise the stability of ^{99m}Tc-tiatide, preparations should not be administered together with other drugs.

6.3 Shelf life

12 months.

After labelling Technetium (^{99m}Tc) tiatide Injection expires after:

- 8 hours , when stored below 25 °C. **6.4 Special precautions for storage**

Technescan MAG3 is to be stored at 2-8 °C. For storage conditions after radiolabelling of the medicinal product, see section 6.3.

IStorage should be in accordance with national regulations for radioactive materials.

6.5 Nature and contents of container.

10 ml Type 1 Ph.Eur glass vial closed with a butyl rubber stopper Ph.Eur and sealed with an aluminium crimpcap. Technescan MAG3 is supplied as five vials in a carton.

6.6 Instructions for use/handling

The contents of the vial is to be labelled with Sodium Pertechnetate (^{99m}Tc) Injection Ph.Eur. After reconstitution with a sodium pertechnetate (^{99m}Tc) solution the diagnostic agent technetium (^{99m}Tc) tiatide is obtained upon heating.

The formation of labelled impurities is minimal, when using an eluate with the smallest possible volume. Therefore, labelling should be done using an eluate with the highest possible radioactive concentration. Only eluates obtained from a ^{99m}Tc-generator, which has been eluted within the preceding 24 hours should be used. Moreover, only eluates obtained from a ^{99m}Tc-generator, which has not been in use for more than one week,

have to be used. Dilution of the preparation should be done with saline. After reconstitution and labelling the solution may be used for one or more administrations.

6.6.1 Instructions for labelling

For labelling it is recommended to use an eluate with the highest possible radioactive concentration, as the formation of labelled impurities is the least when using an eluate with the smallest possible volume.

Elute a ^{99m}Tc generator in a 5 ml volume, according to the fractionated elution technique and follow the directions for use for the generator. Use 3 ml eluate. The desired amount of ^{99m}Tc, with a maximum of 2960 MBq (80 mCi) must be diluted to a volume of 10 ml with a sterile saline solution (0.9%). Add this volume to a vial of Technescan MAG3.

For this a thin needle must be used (G20 or higher) so that the puncture hole closes again. This prevents the water from entering the vial during the heating and cooling steps that follow.

Heat immediately during 10 minutes in a heating block previously heated to 120°C or boiling water bath. During heating the vial should be standing upright in order to prevent traces of metal coming off the rubber stopper, so influencing the labelling procedure unfavourably. Cool down the vial to room temperature in cold water. The preparation is ready for administration. If needed, a dilution with 0.9 % saline solution is possible.

This ^{99m}Tc labelled preparation having a maximum concentration of 2960 MBq per 10 ml can be used until 8 hours after completion of the heating step.

Preferably use eluates obtained by fractionated elution. Follow the pertinent directions for use of the generator.

6.6.2 Precaution during the labelling procedure

To indicate that during the heating and the cooling step no contamination of the contents of the vial has occurred, the user is advised to add a suitable dyestuff to the heating bath and to the cooling bath (e.g. methylene blue to make a concentration of 1 % or sodium fluorescein to make a concentration of 0.1 %). The radiolabelled product vial should be examined for contamination (taking appropriate radiological protective measures) prior to use.

6.6.3 Instructions for quality control

The following methods may be used:

1 HPLC method:

The radiochemical purity of the labelled substance is examined by high performance liquid chromatography (HPLC) using a suitable detector of radioactivity, on a 25 cm RP18 column, flow rate 1.0 ml/min.

Mobile phase A is a 93:7 mixture of phosphate solution (1.36 g KH_2PO_4, adjusted with 0.1 M NaOH to pH 6) and ethanol. Mobile phase B is a 1 : 9

mixture of water and methanol.

Use a elution program with the following parameters:

Time (min):	Flow (ml/min):	%A	%B
10	1	100	0
15	1	0	100

The tiatide peak appears at the end of the passage of mobile phase A. The injection volume is 20 µl and the total count rate per channel must not exceed 30.000.

Requirement:

	t=0	after 8 hours
Tiatide	≥ 95.0%	≥ 94.0%
Total front fractions	≤ 3.0%	≤ 3.0%
Methanol fraction	≤ 4.0%	≤ 4.0%

2 Simplified rapid procedure.

This method may be used as an alternative for the above mentioned methods. The purpose of this method is to check the labelling procedure, as performed by the user in the hospital.

The method is based on cartridges, which are widely used as sample pretreatment of aqueous solutions for chromatography. The cartridge (e.g. Sep-Pak C18, Waters) is washed with 10 ml absolute ethanol, followed by 10 ml 0.001M hydrochloric acid. Remaining residues of the solutions are removed by 5 ml of air.

The Technetium (^{99m}Tc) tiatide solution (e.g. 0.1 ml) is applied on the cartridge. Elute with 5 ml 0.001 M HCl and collect the eluate. Elute with 5 ml of a phosphate buffer (0.01 M, pH=6.0) containing 0.5% ethanol. Add the eluate to the first eluate (together: sum of hydrophilic impurities). Elute the cartridge with 10 ml phosphate buffer (pH=6.0) containing 7% ethanol. This second eluate contains Technetium (^{99m}Tc) tiatide. Finally, elute the cartridge with 10 ml absolute ethanol. This third eluate contains lipophilic impurities.

Measure the radioactivity and calculate the respective percentages. Use the combined eluted radioactivity as 100%.

Requirement: Technetium (^{99m}Tc) tiatide: not less than 90 %.

Hydrophilic impurities: not more than 5%. Lipophilic impurities: not more than 5%.

Other information/precautions:
The administration of radiopharmaceuticals created risks for other persons from external radiation or contamination from spills of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken. Waste must be disposed of according to national regulations for radioactive material.

7 MARKETING AUTHORIZATION HOLDER

Mallinckrodt Medical B.V.
Westerduinweg 3
1755 LE Petten
The Netherlands

8 MARKETING AUTHORIZATION NUMBER

MT 8362

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

31 January 2006 / 10 May 2012

10 DATE OF (PARTIAL) REVISION OF THE TEXT

16.10.2015