ANNEX I

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

SomaKit TOC 40 micrograms kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains 40 micrograms of edotreotide.

The radionuclide is not part of the kit.

Excipient with known effect
The vial of buffer contains approximately 32.5 mg of sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation containing:
- Powder for solution for injection: the vial contains a white lyophilised powder.
- Reaction buffer: the vial contains a clear, colourless solution.

For radiolabelling with gallium (^{68}Ga) chloride solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

After radiolabelling with gallium (^{68}Ga) chloride solution, the solution of gallium (^{68}Ga) edotreotide obtained is indicated for Positron Emission Tomography (PET) imaging of somatostatin receptor overexpression in adult patients with confirmed or suspected well-differentiated gastro-enteropancreatic neuroendocrine tumours (GEP-NET) for localizing primary tumours and their metastases.

4.2 Posology and method of administration

The medicinal product should only be administered by trained healthcare professionals with technical expertise in using and handling nuclear medicine diagnostic agents and only in a designated nuclear medicine facility.

Posology
The recommended activity for an adult weighing 70 kg is 100 to 200 MBq, administered by direct slow intravenous injection.
The activity will be adapted to patient characteristics, the type of PET camera used and acquisition mode.

Elderly population
No special dosage regimen for elderly patients is required.

Renal impairment / Hepatic impairment
The safety and efficacy of gallium (^{68}Ga) edotreotide have not been studied in patients with renal or hepatic impairment.

Paediatric population
The safety and efficacy of gallium (^{68}Ga) edotreotide has not been established in paediatric populations, where the effective dose might be different than in adults. There is no recommendation for use of SomaKit TOC in paediatric patients.

Method of administration
SomaKit TOC is for intravenous use and for single use only.
This medicinal product should be radiolabelled before administration to the patient.

The activity of gallium (^{68}Ga) edotreotide has to be measured with an activimeter immediately prior to injection.

The injection of gallium (^{68}Ga) edotreotide must be administered intravenously in order to avoid local extravasation resulting in inadvertent radiation to the patient and imaging artefacts.

For instructions on extemporaneous preparation of the medicinal product before administration, see sections 6.6 and 12.

For patient preparation, see section 4.4.

Image acquisition
Radiolabelled SomaKit TOC is suitable for PET medical imaging. The acquisition must include a whole body acquisition from skull to mid-thigh. The recommended time for imaging is 40 to 90 minutes post injection. Imaging acquisition start time and duration should be adapted according to the equipment used, the patient and the tumour characteristics in order to obtain the best image quality possible.

4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients listed in section 6.1 or to any of the components of the labelled radiopharmaceutical.

4.4 Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions
If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube must be immediately available.

Individual benefit/risk justification
For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information.

Renal / Hepatic impairment
Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

Paediatric population
For information on the use in paediatric population, see section 4.2.
The safety and efficacy of gallium (^{68}Ga) edotreotide has not been established in paediatric populations, where the effective dose might be different than in adults.

Patient preparation
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 examination in order to reduce radiation.

Interpretation of gallium (^{68}Ga) edotreotide images and limitations of use
PET images with gallium (^{68}Ga) edotreotide reflect the presence of somatostatin receptors in the tissues.

The organs with high physiological uptake of gallium (^{68}Ga) edotreotide include spleen, kidneys, liver, pituitary gland, thyroid gland and adrenals. High physiological uptake of gallium (^{68}Ga) edotreotide by the pancreas uncinate process can also be observed.

In GEP-NET, a more intense gallium (^{68}Ga) edotreotide uptake than normal background is a consistent finding. However, lesions of GEP-NET not expressing sufficient density of somatostatin receptors cannot be visualised with gallium (^{68}Ga) edotreotide. PET images with gallium (^{68}Ga) edotreotide should be interpreted visually, and semiquantitative measurement of gallium (^{68}Ga) edotreotide uptake should not be used for clinical interpretation of images.

Data supporting efficacy of gallium (^{68}Ga) edotreotide for predicting and monitoring of therapeutic response to peptide receptor radionuclide therapy (PRRT) in histologically confirmed metastatic NET are limited (see section 5.1).

In case of Cushing syndrome, a long-term exposure to endogenous hypercortisolism may down regulate somatostatin receptor expression and negatively influence the results of somatostatin receptor imaging with gallium (^{68}Ga) edotreotide. Thus, in patients with GEP-NET and Cushing syndrome, normalisation of hypercortisolism should be suggested before performing PET with gallium (^{68}Ga) edotreotide.

An increased uptake of gallium (^{68}Ga) edotreotide is not specific for GEP-NET. Positive results require evaluating the possibility that another disease, characterised by high local somatostatin receptor concentrations, may be present. As an example, an increase in somatostatin receptor density can also occur in the following pathological conditions: subacute inflammations (areas of lymphocyte concentrations), thyroid diseases (e.g. thyroid autonomy and Hashimoto's disease), tumours of the pituitary gland, neoplasms of the lungs (small-cell carcinoma), meningiomas, mammary carcinomas, lympho-proliferative disease (e.g. Hodgkin's disease and non-Hodgkin lymphomas) and tumours arising from tissue embryologically derived from the neural crest (e.g. paragangliomas, medullary thyroid carcinomas, neuroblastomas, pheochromocytomas).

Splenectomy should also be considered as a relevant factor when reporting the outcome of somatostatin receptor targeted diagnostics.

Concomitant use of somatostatin analogues
It is preferable to perform imaging with gallium (^{68}Ga) edotreotide the day(s) before the next administration of a somatostatin analogue. See section 4.5.

After the procedure
Close contact with infants and pregnant women should be restricted during the first 8 hours after administration.

Specific warnings
Depending on the time when you administer the injection, the content of sodium may in some cases be greater than 1 mmol. This should be taken into account in patient on low sodium diet.

Due to the acidic pH of the radiolabelled gallium (^{68}Ga) edotreotide solution, accidental extravasation may cause local irritation. In case of extravasation, the injection must be stopped, the site of injection must be changed and the affected area should be irrigated with sodium chloride solution.

Precautions with respect to environmental hazard are in section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Somatostatin and its analogues are probably competing to bind to the same somatostatin receptors. Therefore, when treating patients with somatostatin analogues, it is preferable to perform imaging with gallium (^{68}Ga) edotreotide the day(s) preceding the next administration of a somatostatin analogue.
A long-term exposure to endogenous hypercortisolism may down-regulate somatostatin receptor expression and negatively influence the results of somatostatin receptor imaging with gallium (^{68}Ga) edotreotide. In patients with Cushing syndrome, the normalisation of hypercortisolism should be considered before performing PET with SomaKit TOC.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionizing radiation (if there are any) should be offered to the patient.

Pregnancy
No data are available regarding the use of this product during pregnancy. Radionuclide procedures carried out on pregnant women also involve radiation doses to the fœtus. Only essential investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and fœtus.

Breastfeeding
Before administering radiopharmaceuticals to a mother who is breastfeeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding, and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breastfeeding should be interrupted for 8 hours and the expressed feeds discarded.

Close contact with infants should be restricted during the initial 8 hours following injection.

Fertility
No studies were conducted to assess the impact on fertility.

4.7 Effects on ability to drive and use machines

Gallium (^{68}Ga) edotreotide has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

No adverse reactions related to gallium (^{68}Ga) edotreotide have been reported.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is about 4.5 mSv when the maximal recommended activity of 200 MBq is administered, these adverse reactions are expected to occur with a low probability.

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 listed in Appendix V.

4.9 Overdose

In the event of administration of a radiation overdose, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by reinforced hydration and by frequent micturition. It might be helpful to estimate the effective dose that was applied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other diagnostic radiopharmaceuticals for tumour detection, ATC code: V09IX09.

Mechanism of action
Gallium (^{68}Ga) edotreotide binds to somatostatin receptors. *In vitro*, this radiopharmaceutical binds with high affinity mainly to SSTR2 but also, to a lesser extent, to SSTR5.
In vivo, semiquantitative correlation was not assessed between gallium (^{68}Ga) edotreotide uptake in tumours and the density of SSTR in histopathological samples neither in GEP-NET patients nor in normal organs. Moreover, the *in vivo* binding of gallium (^{68}Ga) edotreotide to structures or receptors other than SSTR remains unknown.

Pharmacodynamic effects
At the chemical concentrations used for diagnostic examinations, gallium (^{68}Ga) edotreotide does not appear to have any clinically relevant pharmacodynamic effect.
Edotreotide is a somatostatin analogue. Somatostatin is a neurotransmitter in the central nervous system, but also a hormone which binds to cells of neuroendocrine origin and inhibits the release of growth hormone, insulin, glucagon, and gastrin. There is no data if the intravenous administration of edotreotide produces variation of serum gastrin and serum glucagon levels.

Clinical efficacy and safety
For the detection of the primary GEP-NET site in case of rising levels of a relevant biochemical tumour marker or in case of proven NET metastasis, patient-based sensitivity and specificity of gallium (^{68}Ga) edotreotide PET were 100% (4/4) and 89% (8/9), respectively, in the prospective study of Gabriel et al. 2007. Lesion-detection rate was 75% (3/4) in the subgroup of patients with unknown primary tumour site of the prospective study of Frilling et al. 2010. In the retrospective paper of Schreiter et al. 2014, the intra-individual comparison in a subgroup of 20 patients showed that gallium (^{68}Ga) edotreotide permitted to localise the primary tumour in 9/20 (45%) patients while indium (^{111}In) pentetreotide did in 2/20 (10%).

A prospective intra-individual comparison showed that gallium (^{68}Ga) edotreotide is able to detect lesions better than indium (^{111}In) pentetreotide. A lesion detection rate of 100% (40/40) versus 85% (34/40) was observed in the study of Hofmann et al. 2001 recruiting patients with histologically proven bronchial (n=2) or midgut (n=6) NETs. In the study of Buchmann et al. 2007, conducted in 27 patients mostly with GEP-NET (59%) or NETs of unknown primary (30%), gallium (^{68}Ga) edotreotide identified 279 lesions versus 157 lesions seen with indium (^{111}In) pentetreotide. In the study of Van Binnebeek et al. 2015 in 53 patients with metastatic GEP-NET [mostly GEP-NET (n=39) or NET of unknown origin (n=6)], the lesion-based detection rate of gallium (^{68}Ga) edotreotide was 99.9% (1098/1099) versus 60% (660/1099) for indium (^{111}In) pentetreotide based on the follow-up scans. In the study of Lee et al. 2015 in 13 GEP-NET patients, a total of 35 positive lesions were

detected in 10 patients on either gallium (^{68}Ga) edotreotide PET/CT or indium (^{111}In) pentetreotide SPECT/CT while 3 patients did not exhibit any positive lesions on either imaging method. Gallium (^{68}Ga) edotreotide detected 35/35 (100%) lesions vs 19/35=54% for indium (^{111}In) pentetreotide SPECT/CT. In the study of Kowalski et al. 2003 in 4 patients with GEP-NET, gallium (^{68}Ga) edotreotide showed better patient-based detection rate (100%) than indium (^{111}In) pentetreotide (50%).

Data available on clinical efficacy of gallium (^{68}Ga) edotreotide for the indication of predicting and monitoring of therapeutic response to peptide receptor radionuclide therapy (PRRT) in histologically confirmed metastatic NET are limited. Five studies have been submitted, one of them prospective (Gabriel et al. 2009) and four retrospective studies (Kroiss et al. 2013, Ezziddin et al. 2012, Kratochwil et al. 2015 and Luboldt et al.2010a). In the study by Gabriel et al. 2009 pre-PRRT gallium (^{68}Ga) edotreotide was compared with CT or MRI using the Response Evaluation Criteria in Solid Tumors (RECIST). Gallium (^{68}Ga) edotreotide PET and CT showed a concordant result in 32 patients (70%) and discrepancies in 14 patients (30%) presenting 9 with progressive disease and 5 with remission.

The retrospective study of Kroiss et al. 2013 in 249 NET patients showed that PRRT does not significantly influence semiquantitative uptake of gallium (^{68}Ga) edotreotide PET, except in liver metastases of patients with NET, but the study lacked histological confirmation. The three remaining retrospective studies recruited small samples (ranging from 20 to 28 GEP-NET patients or those with cancer of unknown origin) and found that semiquantitative uptake in the pre-PRRT gallium (^{68}Ga) edotreotide PET scan correlated with the tumour-absorbed doses per injected activity of the subsequent first treatment cycle, differed between those lesions classified as responding and non-responding after three PRRT cycles, and helped to separate hepatic metastases from normal liver tissue.

5.2 Pharmacokinetic properties

Distribution
After intravenous injection, gallium (^{68}Ga) edotreotide is rapidly cleared from the blood following bi-exponential elimination of activity with half-lives of 2.0 ± 0.3 min and 48 ± 7 min respectively.

Organ uptake
The organ with the highest physiological uptake of gallium (^{68}Ga) edotreotide is the spleen, followed by the kidneys. The uptake in the liver and in the pituitary, thyroid and adrenal glands is lower. High physiological uptake of gallium (^{68}Ga) edotreotide by the pancreas uncinate process can also be observed. About 50 minutes after intravenous administration, gallium (^{68}Ga) edotreotide accumulation shows plateauing in all organs.
The organ uptake has been shown to be age-independent in normal adult human tissues and also predominantly gender-independent (except for the thyroid and head of pancreas).

Elimination
No radioactive metabolites were detected in serum within 4 hours after intravenous injection of gallium (^{68}Ga) edotreotide.
Approximately 16% of gallium (^{68}Ga) edotreotide activity is removed from the body in the urine within 2 to 4 hours. The peptide is excreted via kidneys as intact compound.

Half-life
Given that the elimination rate is substantially slower than the physical half-life of gallium (^{68}Ga) (68 min), the biological half-life will have little impact on the effective half-life of the product which then would be expected to be somewhat less than 68 minutes.

Renal/Hepatic impairment
The pharmacokinetics in patients with renal or hepatic impairment has not been characterized.

5.3 Preclinical safety data

Non-clinical data did not reveal any special hazard for gallium (^{68}Ga) edotreotide in humans.

Local tolerance assessment resulted in mild to moderate inflammation signs in the perivascular region of some animals which can be attributed to the acidic pH of the solution.

No studies on fertility, embryology, mutagenicity or long-term carcinogenicity have been conducted.

Regarding the novel excipient (1,10-phenanthroline), during the toxicity study conducted with the kit formulation of SomaKit TOC including 1,10-phenanthroline at a dose 400 fold higher than the human dose, no toxicity signs were observed.

Genotoxicity studies on 1,10-phenanthroline available in the literature show negative results in bacterial mutation assay (Ames test), while in a mouse lymphoma assay an indication of possible genotoxicity was obtained at concentrations 750 times higher than the maximum 1,10-phenanthroline blood concentration achievable in patients. However, even taking as worst case reference the limits for genotoxic and carcinogenic impurities, the risk related to the trace amounts of 1,10-phenanthroline in SomaKit TOC formulation is considered negligible at the dose to be administered in patients: the exposure to 1,10-phenanthroline (5 µg/dose) is 24 fold lower than the acceptable daily intake for a genotoxic impurity (120 µg/day for exposures <1 month).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

1,10-phenanthroline
Gentisic acid
Mannitol (E421)

Buffer

Formic acid
Sodium hydroxide (E524)
Water for injections

After radiolabelling, the solution obtained also contains, as excipient, hydrochloric acid from the generator eluate.

6.2 Incompatibilities

Radiolabelling of carrier molecules with gallium (^{68}Ga) chloride is very sensitive to the presence of trace metal impurities. Only syringe and syringe needles able to minimise trace metal impurity levels (for example, non-metallic or coated with silicone needles – not supplied –) should be used.

This medicinal product must not be mixed with other products except those mentioned in section 12.

6.3 Shelf life

Kit as packaged for sale
12 months.

After radiolabelling
4 hours.
Do not store above 25°C after radiolabelling.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Store in the original package in order to protect from light.
For storage conditions after radiolabelling of the medicinal product, see section 6.3.

Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container and special equipment for use

Each pack contains:

- One vial of powder for solution for injection: 10 ml Type I glass vial closed with a chlorobutyl rubber stopper and sealed with a flip-off cap. Each vial contains 40 micrograms of edotreotide.
- One vial of buffer: 10 ml cyclic olefin polymer vial closed with a teflon stopper and sealed with a flip-off cap. Each vial contains 1 ml of reaction buffer.

6.6 Special precautions for disposal and other handling

General warnings
Radiopharmaceuticals should be received, used and administered only by authorized persons in designated clinical settings. Their receipt, storage, use, transfer, and disposal are subject to the regulations and/or appropriate licenses of the competent official organization.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

Contents of the vials are intended only for use in the preparation of gallium (^{68}Ga) edotreotide solution for injection and are not to be administered directly to the patient without first undergoing the preparative procedure.

Each 40 microgram vial contains an excess of product. However, it is recommended that the vial be prepared as instructed and used for a single patient dose, based on the activity to be injected; any remaining material should be discarded after radiolabelling and use.

Precautions to be taken before handling or administration of the medicinal product
For instructions on radiolabelling of the medicinal product before administration, see section 12.

If at any time in the preparation of this product the integrity of the vials is compromised it should not be used.

Administration procedures should be carried out in a way to minimize risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The content of the kit before radiolabelling is not radioactive. However, after gallium (^{68}Ga) chloride solution is added, adequate shielding of the final preparation must be maintained.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting, blood, etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

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

7. MARKETING AUTHORISATION HOLDER

Advanced Accelerator Applications
20 rue Diesel
01630 Saint Genis Pouilly
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1141/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08/12/2016

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY

Gallium-68 decays with a half-life of 68 min to stable zinc-68, 89% through positron emission with a mean energy of 836 keV followed by photonic annihilation radiations of 511 keV (178%), 10% through orbital electron capture (X-ray or Auger emissions), and 3% through 13 gamma transitions from 5 excited levels.

The dosimetry of gallium (^{68}Ga) edotreotide was calculated by Sandstrom et al. (2013), using OLINDA/EXM 1.1 software (table 1).

Table 1: Dosimetry of gallium (^{68}Ga) edotreotide

Absorbed dose in selected organs	**mGy/MBq**
Organs	**Mean**
Adrenals	0.077
Brain	0.010
Breasts	0.010
Gallbladder wall	0.015
Lower large intestine wall	0.015
Small intestine	0.023
Stomach wall	0.013
Upper large intestine wall	0.020
Heart wall	0.020
Kidneys	0.082
Liver	0.041
Lungs	0.007
Muscle	0.012
Ovaries	0.015
Pancreas	0.015
Red marrow	0.016
Osteogenic cells	0.021
Skin	0.010
Spleen	0.108
Testes	0.011
Thymus	0.011

Absorbed dose in selected organs	mGy/MBq
Organs	**Mean**
Thyroid	0.011
Urinary bladder wall	0.119
Uterus	0.015
Total body	0.014
Effective dose mSv/MBq	0.021

The effective dose resulting from the administration of an activity of 200 MBq to an adult weighing 70 kg is about 4.2 mSv.
For an administered activity of 200 MBq the typical radiation dose to the critical organs, which are the urinary bladder wall, the spleen, the kidneys and the adrenals, are about 24, 22, 16 and 15 mGy, respectively.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Radiation safety – Product handling
Use waterproof gloves, effective radiation shielding, and appropriate safety measures when handling the radiolabelled SomaKit TOC to avoid unnecessary radiation exposure to the patient, occupational workers, clinical personnel, and other persons.

Radiopharmaceuticals should be used by or under the control of healthcare professionals who are qualified by specific training and experienced in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorised to license the use of radionuclides.

The gallium (^{68}Ga) edotreotide solution must be prepared in accordance with radioprotection and pharmaceutical quality standards, especially concerning aseptic technique. If at any time in the preparation of this product the integrity of the vials is compromised, the product should not be used.

A low dead space 1 ml plastic syringe must be used in order to precisely measure the adequate volume of reaction buffer to be added during the preparation. Glass syringe must not be used.

For administration, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system.

Method of preparation
SomaKit TOC is supplied as a kit containing two vials. It is intended to be radiolabelled with a gallium (^{68}Ga) chloride solution compliant with the Ph. Eur. monograph 2464 *Gallium (^{68}Ga) chloride solution for radiolabelling* and that, in addition, is sterile and has been tested for compatibility with SomaKit TOC. Only generators that have been authorised as medicinal products in the EU should be used. Refer to the Summary of Product Characteristics of the particular generator for more information.

The following authorised generator has shown to be compatible with SomaKit TOC:
GalliaPharm, 0.74 – 1.85 GBq, radionuclide generator (Eckert & Ziegler Radiopharma GmbH).

The gallium (^{68}Ga) edotreotide solution for intravenous injection must be prepared according to aseptic procedure, local regulation and the following instructions:

a. If possible, for more convenience in the preparation of radiolabelled SomaKit TOC, the heating platform should be placed right beside the generator.

b. Set the temperature of the shielded dry bath at 95°C and wait for the temperature to reach the set point and stabilize.

c. Flip off cap from the vial of powder and swab the top of the vial closure with an appropriate antiseptic to disinfect the surface, and then allow the stopper to dry.

d. Pierce the Vial 1 septum with a 0.2 µm sterile vent filter in order to maintain atmospheric pressure within the vial during the radiolabelling process.

e. Flip off cap from the Vial 2 (Reaction buffer) and swab the top of the vial closure with an appropriate antiseptic to disinfect the surface, and then allow the stopper to dry. With a low dead space 1 ml sterile syringe carefully withdraw the adequate volume of the reaction buffer, calculated as follows:

buffer volume (ml) = HCl volume (ml) x HCl molarity

and keep the reaction buffer in syringe for step "i"

f. Connect the male luer of the outlet line of the $^{68}Ge/^{68}Ga$ generator with a sterile needle (coated with silicone or other appropriate material able to reduce metal impurity trace, – not supplied).

g. Connect the Vial 1 to the outlet line of the generator by pushing the needle through the rubber septum.

h. Elute the generator directly into the Vial 1 (through the needle) according to the generator manufacturer instructions for use, in order to reconstitute the powder with the eluate. The elution can be performed either manually or by means of a pump.

i. At the end of the elution, disconnect the generator from the Vial 1 withdrawing the needle from the rubber septum and immediately add the reaction buffer previously dosed in the 1 ml sterile syringe. Withdraw the syringe and the 0.2 µm sterile vent filter and move the vial to the hole of the dry bath at 95°C, using a plier. Leave the vial at 95°C for at least 7 minutes (do not exceed 10 minutes heating) without agitation or stirring.

j. After 7 minutes, remove the vial from the dry bath, place it in an appropriately labelled lead shield and let it cool down at room temperature for approximately 10 minutes.

k. Assay the vial radioactivity using a suitable radioactivity calibration system and record the result. Report the activity value, the calibration time, the batch number and the expiry time on the shield label included in the pack to be applied on the lead shielding container after radiolabelling.

l. Perform the quality control according to the recommended methods in order to check the compliance to the specifications (see section, "Quality control").

m. The solution should be visually inspected prior to use. Only clear solutions, free from visible particles should be used. The visual inspection should be performed under a shielded screen for radioprotection purposes.

n. Store the vial containing the gallium (^{68}Ga) edotreotide solution below 25°C until use. At the time of administration the product must be aseptically withdrawn and the radioprotection standards must be followed. The patient dose should be measured by a suitable radioactivity calibration system immediately prior to patient administration. Product administration data should also be recorded.

Gallium (^{68}Ga) edotreotide solution is stable up to 4 hours after preparation. Therefore, the radiolabelled solution can be used within 4 hours after preparation according to the radioactivity required for the administration.

Radioactive waste must be disposed of in accordance with relevant national regulations.

After radiolabelling with the correct volume of reaction buffer and generator eluate, any further dilution with any diluent is prohibited.

A schematic representation of the radiolabelling procedure is shown in Figure 1.

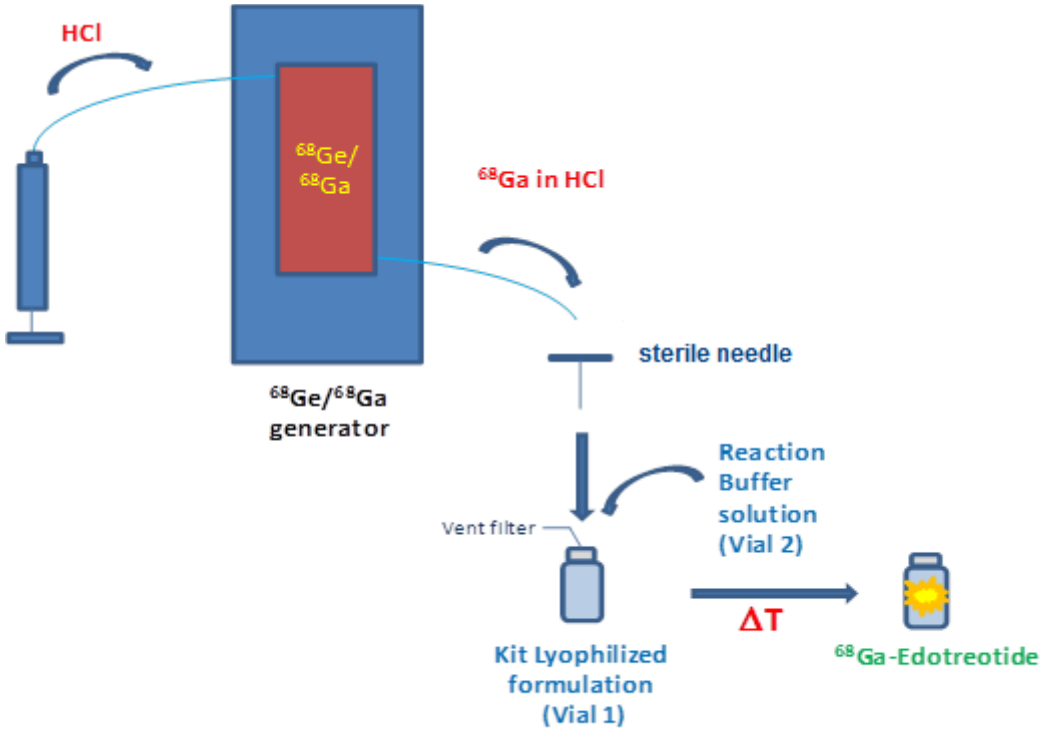

Figure 1: Radiolabelling procedure

Quality control

Table 2: Specifications of the gallium (^{68}Ga) edotreotide

Test	**Acceptance Criteria**	**Method**
Appearance	Clear solutions free of visible particles	Visual inspection
pH	3.2 – 3.8	pH-indicator strips
Labelling efficiency colloidal gallium-68 species	≤ 3%	Thin layer chromatography (ITLC1, see details below)
Labelling efficiency % Free gallium-68	≤ 2%	Thin layer chromatography (ITLC2, see details below)

The quality controls should be performed under a shielded screen for radioprotection purposes.

Recommended method for determining labelling efficiency of gallium (^{68}Ga) edotreotide:

ITLC1:
Material

- Glass-fibre ITLC paper (e.g. Agilent ITLC SGI001) pre-cut to 1 cm x 12 cm strips
- Mobile phase: 77 g/L solution of ammonium acetate in water /Methanol 50:50 V/V
- Developing tank
- Radiometric ITLC scanner

Sample Analysis

a. The TLC developing tank is prepared by pouring the mobile phase to a depth of 3 to 4 mm. Cover the tank and allow to equilibrate.

b. Apply a drop of the gallium (^{68}Ga) edotreotide on a pencil line 1 cm from the bottom of the ITLC strip.
c. Place the ITLC strip in the developing tank and allow it to develop for a distance of 9 cm from the point of application.
d. Scan the ITLC with a radiometric ITLC scanner
e. The retention factor (Rf) specifications are as follows:
Not complexed gallium (^{68}Ga) = 0 to 0.1
gallium (^{68}Ga) edotreotide = 0.8 to 1

The labelling efficiency is calculated by integration of peak with Rf = 0 to 0.1 that must be ≤ 3%.

ITLC2:
Material

- Glass-fibre ITLC paper (e.g. Agilent ITLC SGI001) pre-cut to 1 cm x 12 cm strips Mobile phase: sodium Citrate 0.1 M (pH 5) in water
- Developing tank
- Radiometric ITLC scanner

Sample Analysis

a. The TLC developing tank is prepared by pouring the mobile phase to a depth of 3 to 4 mm. Cover the tank and allow to equilibrate.
b. Apply a drop of the gallium (^{68}Ga) edotreotide solution on a pencil line 1 cm from the bottom of the ITLC strip.
c. Place the ITLC strip in the developing tank and allow it to develop for a distance of 9 cm from the point of application.
d. Scan the ITLC with a radiometric ITLC scanner
The retention factor (Rf) specifications are as follows: gallium (^{68}Ga) edotreotide = 0.1 to 0.2
Free gallium-68 = 0.9 to 1

The labelling efficiency is calculated by integration of peak with Rf = 0.9 to 1.0 that must be ≤ 2%.

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE
B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
Gipharma S.r.l.
Via Crescentino
13040 Saluggia (VC)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

SomaKit TOC 40 micrograms kit for radiopharmaceutical preparation
edotreotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 40 micrograms of edotreotide

3. LIST OF EXCIPIENTS

Excipients:

Powder: 1,10-phenanthroline, gentisic acid, mannitol (E421)

Buffer: formic acid, sodium hydroxide (E524), water for injections

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Kit for radiopharmaceutical preparation
The box contains:
- 1 vial of powder
- 1 vial of buffer

5. METHOD AND ROUTE(S) OF ADMINISTRATION

To be radiolabelled with the reaction buffer and a solution of Gallium-68 (^{68}Ga) in HCl provided by a germanium (^{68}Ge)/gallium (^{68}Ga) generator.

Intravenous use after radiolabelling.
For single use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Medicinal product radioactive after radiolabelling.

8. EXPIRY DATE

EXP

After radiolabelling, use within 4 hours.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Store in the original package in order to protect from light.

After radiolabelling, store below 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Radioactive waste must be disposed of in accordance with relevant national regulations.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Advanced Accelerator Applications
20 rue Diesel
01630 Saint Genis Pouilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1141/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

SomaKit TOC 40 micrograms powder for solution for injection
edotreotide
IV after radiolabelling

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 micrograms

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BUFFER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

SomaKit TOC
Reaction buffer

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SHIELD LABEL TO BE APPLIED AFTER RADIOLABELLING

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

SomaKit TOC 40 micrograms solution for injection
Gallium (^{68}Ga) edotreotide
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

Use within 4 hours after radiolabelling.

EXP: _____ Time/Date

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Total activity: _____MBq
Total volume: _____mL
Calibration time: _____ Time/Date

6. OTHER

Do not store above 25ºC

B. PACKAGE LEAFLET

Package leaflet: Information for the user

SomaKit TOC 40 micrograms kit for radiopharmaceutical preparation
Edotreotide

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your nuclear medicine doctor who will supervise the procedure.
- If you get any side effects, talk to your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What SomaKit TOC is and what it is used for

This medicine is a radiopharmaceutical product for diagnostic use only. It contains the active substance edotreotide. Before it can be used, the powder in the vial is mixed with a radioactive substance called gallium (^{68}Ga) chloride to make gallium (^{68}Ga) edotreotide (this procedure is called radiolabelling).

Gallium (^{68}Ga) edotreotide contains a small amount of radioactivity. After injection into a vein, it can make parts of the body areas visible to doctors during a medical imaging procedure called positron emission tomography (PET). This medical procedure obtains images of your organs, to help locate the abnormal cells or tumours giving valuable information about your disease.

The use of SomaKit TOC involves exposure to small amounts of radioactivity. Your doctor and the nuclear medicine doctor have considered that the clinical benefit from the procedure with the radiopharmaceutical outweighs the risk due to radiation.

2. What you need to know before SomaKit TOC is used

SomaKit TOC must not be used
- if you are allergic to edotreotide or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your nuclear medicine specialist before you are given SomaKit TOC:
- if you experience any signs of allergic reaction (listed in section 4) after previous administration of SomaKit TOC;
- if you have kidney or liver problems (renal or hepatic disease);
- if you are under 18 years of age;
- if you have signs of dehydration before and after the examination;

- if you have others medical conditions, such as high level of cortisol in the body (Cushing syndrome), inflammation, thyroid disease, other type of tumour (of pituitary gland, lung, brain, breast, immune system, thyroid, adrenal gland or others) or disease of spleen that may affect the interpretation of the images;
- if you have been taking other medicines, such as somatostatin analogues and glucocorticoids, which may interact with SomaKit TOC;
- if you are pregnant or believe you may be pregnant;
- If you are breast-feeding.

Your nuclear medicine doctor will inform you if you need to take any other special precaution before or after using SomaKit TOC.

Before administration of SomaKit TOC
You should drink plenty of water before the start of the examination in order to urinate as often as possible during the first hours after the procedure to ensure that SomaKit TOC is removed as quickly as possible from the body.

Children and adolescents
This medicine is not recommended in patients under 18 years of age because its safety and efficacy have not been established in this patient population.

Other medicines and SomaKit TOC
Tell your nuclear medicine doctor if you are taking, have recently taken or might take any other medicines, including somatostatin analogues, glucocorticoids (also called corticosteroids), since they may interfere with the interpretation of the images. If you are taking somatostatin analogues you might be asked to stop your treatment for a short period of time.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your nuclear medicine doctor for advice before you are given this medicine.

You must inform the nuclear medicine doctor before the administration of SomaKit TOC if there is a possibility you might be pregnant, if you have missed your period or if you are breast-feeding.
When in doubt, it is important to consult your nuclear medicine doctor who will supervise the procedure.

There is no information about the safety and the efficacy of the use of this medicine during pregnancy. Only essential investigations should be carried out during pregnancy, when the likely benefit far exceeds any risk to the mother and foetus.

If you are breast-feeding the nuclear medicine doctor may either delay the medical procedure until you no longer breast-feed or ask you to stop breastfeeding and to discard this milk until there is no radioactivity in your body (8 hours after the administration of SomaKit TOC).
Please ask your nuclear medicine doctor when you can resume breast-feeding.

Driving and using machines
It is considered unlikely that SomaKit TOC will affect your ability to drive or to use machines.

SomaKit TOC contains sodium
This medicine contains 1.5 mmol (or 32.5 mg) sodium per dose. Take this into consideration if you are on a controlled sodium diet.

3. How SomaKit TOC is used

There are strict laws on the use, handling and disposal of radiopharmaceutical products. SomaKit TOC will only be used in special controlled areas. This product will only be handled and given to you by

people who are trained and qualified to use it safely. These persons will take special care for the safe use of this product and will keep you informed of their actions.

The nuclear medicine doctor supervising the procedure will decide on the quantity of SomaKit TOC to be used in your case. It will be the smallest quantity necessary to get the desired information.
The quantity to be administered usually recommended for an adult ranges from 100 MBq to 200 MBq (megabecquerel, the unit used to express radioactivity).

Administration of SomaKit TOC and conduct of the procedure
After radiolabelling, SomaKit TOC is administered by intravenous injection.
A single injection is sufficient to conduct the test that your doctor needs.
After injection, you will be offered something to drink and asked to urinate immediately preceding the test.

Duration of the procedure
Your nuclear medicine doctor will inform you about the usual duration of the procedure.

After administration of SomaKit TOC, you should:
- avoid any close contact with young children and pregnant women for 8 hours after the injection
- urinate frequently in order to eliminate the product from your body.

The nuclear medicine doctor will inform you if you need to take any special precautions after receiving this medicine. Contact your nuclear medicine doctor if you have any questions.

If you have been given more SomaKit TOC than you should
An overdose is unlikely because you will only receive a single dose under controlled conditions by the nuclear medicine doctor supervising the procedure. However, in the case of an overdose, you will receive the appropriate treatment. Drinking and emptying your bladder frequently will help remove the radioactive substance from your body more quickly.

Should you have any further questions on the use of SomaKit TOC, please ask the nuclear medicine doctor who supervises the procedure.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Although no side effects have been reported, a potential risk of allergic reactions (hypersensitivity) exists with SomaKit TOC. Symptoms may include: warm flush, redness of the skin, swelling, itching, nausea and difficulty breathing. In case of allergic reactions you will receive the appropriate treatment from your medical staff.

This radiopharmaceutical will deliver low amounts of ionising radiation associated with the least risk of cancer and hereditary abnormalities.

Reporting of side effects
If you get any side effects talk to your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How SomaKit TOC is stored

You will not have to store this medicine. This medicine is stored under the responsibility of the specialist in appropriate premises. Storage of radiopharmaceuticals will be in accordance with national regulation on radioactive materials.

The following information is intended for the specialist only.

Keep this medicine out of the sight and reach of children.

SomaKit TOC must not be used after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).
Store in the original package in order to protect from light.

After radiolabelling, SomaKit TOC should be used within 4 hours. Do not store above 25°C after radiolabelling.

SomaKit TOC must not be used if there are visible signs of deterioration.

Do not throw away any medicines via wastewater or household waste. Wait for the level of radioactivity to decay adequately before throwing away radioactive products. These measures will help protect the environment.

6. Contents of the pack and other information

What SomaKit TOC contains
- The active substance is edotreotide. One vial of powder contains 40 µg of edotreotide.
- The other ingredients are: 1,10-phenanthroline, gentisic acid, mannitol, formic acid, sodium hydroxide, water for injections.

SomaKit TOC contains sodium (see section 2).

After radiolabelling, the solution obtained also contains hydrochloric acid.

What SomaKit TOC looks like and contents of the pack
SomaKit TOC is a kit for radiopharmaceutical preparation containing:
- A glass vial with black flip-off cap containing a white powder.
- A glass vial with yellow flip-off cap containing a clear and colourless solution.

The radioactive substance is not part of the kit and should be added during the preparation steps before injection.

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fax: +33 4 50 99 30 71
e-mail: info@adacap.com

Manufacturer
Gipharma S. r.l.
Via Crescentino,

13040 Saluggia (VC)
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in
Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

The following information is intended for healthcare professionals only:

The complete SmPC of SomaKit TOC is provided as a separate document in the product package, with the objective to provide healthcare professionals with other additional scientific and practical information about the administration and use of this radiopharmaceutical.

Please refer to the SmPC.