ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lymphoseek 50 micrograms kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 micrograms of tilmanocept.
The radionuclide is not part of the kit.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.

The vial contains a sterile, non-pyrogenic, white to off-white lyophilized powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Radiolabelled Lymphoseek is indicated for imaging and intraoperative detection of sentinel lymph nodes draining a primary tumour in adult patients with breast cancer, melanoma, or localised squamous cell carcinoma of the oral cavity.

External imaging and intraoperative evaluation may be performed using a gamma detection device.

4.2 Posology and method of administration

This medicinal product is restricted to hospital use only.

The medicinal product should only be administered by trained healthcare professionals with technical expertise in performing and interpreting sentinel lymph node mapping procedures.

Posology

The recommended dose is 50 micrograms tilmanocept radiolabelled with technetium Tc 99m at 18.5 MBq for same day surgery or 74 MBq for next day surgery. The dose of 50 micrograms should not be adjusted for body weight differences. The total injection amount should not exceed 50 micrograms tilmanocept, with a total maximum radioactivity of 74 MBq per dose.

The recommended minimum time for imaging is 15 minutes post injection. Intraoperative lymphatic mapping may begin as early as 15 minutes post injection.

Patients scheduled for surgery on the day of injection will receive 18.5 MBq technetium Tc 99m radiolabelled product. Administration should occur within 15 hours of the scheduled time of the surgery and intraoperative detection.

Patients scheduled for surgery on the day after injection will receive 74 MBq technetium Tc 99m radiolabelled product. Administration should occur within 30 hours of the scheduled time of the surgery and intraoperative detection.

Special populations

Hepatic or renal impairment

Careful consideration of the activity to be administered in these patients is required since an increased radiation exposure is possible. The radiation dose to the patient would not exceed 2.28 mSv even if none of a 74 MBq dose were eliminated.

Extensive dose-range and adjustment studies with the medicinal product in normal and special populations have not been performed. The pharmacokinetics of technetium Tc 99m tilmanocept in patients with renal or hepatic impairment have not been characterised (see section 5.2).

Elderly population

Elderly patients aged 65 or older (32%) were evaluated in clinical studies; no safety issues were identified. No dose adjustment is recommended based on age.

Paediatric population

The safety and efficacy of Lymphoseek in children and adolescents below the age of 18 years has not yet been established. No data are available.

Method of administration

This medicinal product must be radiolabelled before administration to the patient. The radiolabelled product is a clear, colourless solution with no visible particles.

Following radiolabelling, administration can be by either intradermal, subcutaneous, intratumoural, or peritumoural injection.

For melanoma, administration is intradermal in single or multiple divided injections.

For breast cancer, administration is intradermal, subareolar (single or multiple divided injections) or peritumoural (multiple divided injections).

For squamous cell carcinoma of the oral cavity, administration is peritumoural (multiple divided injections).

Each 50 microgram vial contains an additional overfill to ensure that 50 micrograms of tilmanocept can be delivered. However, it is required that the vial be prepared as instructed and a 50 microgram aliquot be used for a single patient dose.

Individual injection volumes should not exceed 0.5 mL or be less than 0.1 mL. Total injection volume should be no greater than 1.0 mL and no less than 0.1 mL. Dilution of the product in volumes greater than 1.0 mL could affect the *in vivo* disposition of Lymphoseek.

For instructions for preparation and control of the radiochemical purity of the radiopharmaceutical, see section 12.

For patient preparation, see section 4.4.

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 radiolabelled product.

4.4 Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions
The possibility of hypersensitivity including severe life-threatening fatal anaphylactic / anaphylactoid reactions must always be considered.

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 and ventilator 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 and hepatic impairment
Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible. The estimated radiation dose to the patient would not exceed 2.28 mSv even if none of a 74 MBq dose were eliminated (see section 4.2).

Patient preparation
The patient should be well hydrated before the start of the examination and frequent voiding of urine during the initial hours after examination would reduce radiation exposure to the patient.

Specific warnings
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

For precautions with respect to environmental hazard, see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Adding very large volumes of tracing agents or other injectants temporally or anatomically proximal to Lymphoseek could affect the *in vivo* disposition of Lymphoseek. Additional tracing agents should not be injected within 30 minutes of Lymphoseek administration.

No interaction studies have been performed.

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 ionising radiation (if there are any) should be offered to the patient.

Pregnancy
There are no data from the use of Lymphoseek in pregnant women. No reproductive toxicity studies in animals were performed, and it is not known if Lymphoseek can cause foetal harm when administered to a pregnant woman.

Radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus. Only essential investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and foetus.

Breast-feeding
It is not known whether technetium Tc 99m tilmanocept is excreted into human milk.

Before administering radiopharmaceuticals to a mother who is breast-feeding consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breast-feeding, and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If administration is considered necessary, breast-feeding should be interrupted for 24 hours post injection and the expressed feeds discarded.

Fertility
Animal fertility studies have not been conducted with Lymphoseek.

4.7 Effects on ability to drive and use machines

Lymphoseek has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

In clinical trials with 553 patients, the most common adverse reactions were:
- Injection site irritation (0.7%; 4 of 553 patients)
- Injection site pain (0.2%; 1 of 553 patients)

Other adverse reactions were uncommon, and of mild severity and short duration.

Tabulated list of adverse reactions

Clinical studies have evaluated the incidence of adverse reactions listed below in 553 subjects 18 years and above who received Lymphoseek. These reactions were temporally related to Lymphoseek administration and could be due to other medicinal products administered to patients or surgical procedures.

Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (frequency cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class (SOC)	**Adverse Drug Reaction (ADR)**
Metabolism and nutrition disorders	Uncommon: Hypercalcaemia
Nervous system disorders	Uncommon: Aphasia, Dizziness, Headache, Paraesthesia
Eye disorders	Uncommon: Vision blurred
Cardiac disorders	Uncommon: Sinus tachycardia
Vascular disorders	Uncommon: Flushing
Gastrointestinal disorders	Uncommon: Nausea
Skin and subcutaneous tissue disorders	Uncommon: Skin irritation
Musculoskeletal and connective tissue disorders	Uncommon: Pain in extremity, Musculoskeletal pain, Neck pain, Pain in jaw
Renal and urinary disorders	Uncommon: Micturition urgency, Pollakiuria

Reproductive system and breast disorders	Uncommon: Breast pain
General disorders and administration site conditions	Uncommon: Injection site irritation, Injection site pain, Feeling hot
Injury, poisoning and procedural complications	Uncommon: Incision site pain, Seroma, Wound dehiscence

Exposure to ionizing radiation is linked with cancer induction and a potential for the development of hereditary defects. As the effective dose to an adult (70 kg) is 1.32 mSv when the maximal recommended activity of 74 MBq is administered 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

The total injection amount should not exceed 50 micrograms tilmanocept, with a total maximum radioactivity of 74 MBq per dose. Chronic or acute overdose is unlikely to occur given the total injection amount.

No clinical consequences were observed at dose levels of 3.7 times the recommended dose of Lymphoseek in humans, or at 390 times the anticipated human exposure of tilmanocept in animals.

In the event of administration of a radiation overdose with tilmanocept the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceutical, tumour detection, ATC Code: V09IA09.

Mechanism of action
Lymphoseek is a receptor-targeted radiopharmaceutical that is designed to rapidly transit lymphatic vessels; it biotargets, accumulates, and is retained in primary, key predictive, draining lymph nodes (sentinel lymph nodes). The substance, tilmanocept, specifically binds to mannose binding receptor proteins (CD206) that reside on the surface of macrophages and dendritic cells. Macrophages are present in high concentrations in lymph nodes.

Tilmanocept is a macromolecule consisting of multiple units of diethylenetriaminepentaacetic acid (DTPA) and mannose, each synthetically attached to a 10 kDa dextran backbone. The mannose acts as a substrate for the receptor, and the DTPA serves as a chelating agent for labelling with technetium Tc 99m. The mean diameter of tilmanocept is 7 nm and this small molecular size permits enhanced transit into lymphatic channels resulting in rapid and consistent injection site clearance.

Following reconstitution and labelling, Lymphoseek is intended to be injected in close proximity to the tumour and used in preoperative gamma detection imaging in conjunction with a stationary gamma camera (scintigraphy), single photon emissioncomputed tomography (SPECT), or SPECT/computerized tomography SPECT/CT, and/or intraoperatively in conjunction with a gamma detection probe to localise sentinel lymph nodes in the lymphatic pathway draining the tumour.

In *in vitro* studies, technetium Tc 99m tilmanocept exhibited specific and tight binding to human CD206 receptors with a primary binding site affinity of K_d = 2.76 x x 10^{-11} M. In Phase 1 clinical studies, approximately 0.5 to 1.8% of the dose is accumulated in draining lymph nodes through specific binding after 30 minutes. Technetium Tc 99m tilmanocept binding is independent of tumour type or severity.

Clinical efficacy

In Phase 3 clinical studies, technetium Tc 99m tilmanocept was detectable in sentinel lymph nodes within 10 minutes. In external gamma imaging analysis, bound technetium Tc 99m tilmanocept has been shown to be retained in the same draining lymph nodes for up 30 hours. Preoperative lymphoscintigraphy was performed in 100% of melanoma patients, 100% of head and neck squamous cell carcinoma patients, and 82% of breast cancer patients. The overall rate of agreement between lymph node localisation (determined by radioactivity detection) on preoperative lymphoscintigraphy and intraoperative lymph node survey was 97.8% for all patients.

In Phase 3 clinical studies in breast cancer patients mapped with both technetium Tc 99m tilmanocept and vital blue dye, technetium Tc 99m tilmanocept localised in 99.91% of patients with a mean 2.08 localised sentinel lymph nodes per patient by fixed effects meta-analyses. These rates were significantly greater ($p<0.0001$) against a random effects meta-analysis of localisation rates from published literature for colloidal lymphatic mapping agents as used in European clinical practice. In a fixed effects meta-analysis of two Phase 3 studies, technetium Tc 99m tilmanocept localised in 99.99% of the excised lymph nodes stained blue by a vital blue dye (concordance). Alternatively, vital blue dye localised in 66.96% of the excised lymph nodes detected by technetium Tc 99m tilmanocept (reverse concordance).

In Phase 3 clinical studies in melanoma patients mapped with both technetium Tc 99m tilmanocept and vital blue dye, technetium Tc 99m tilmanocept localised in 99.89% of patients with a mean 2.30 localised sentinel lymph nodes per patient by fixed effects meta-analyses. These rates were significantly greater ($p<0.0001$) against a random effects meta-analysis of localisation rates from published literature for colloidal lymphatic mapping agents as used in European clinical practice. In a fixed effects meta-analysis of two Phase 3 studies, technetium Tc 99m tilmanocept localised in 99.99% of the excised lymph nodes stained blue by a vital blue dye (concordance). Alternatively, vital blue dye localised in 63.50% of the excised lymph nodes detected by technetium Tc 99m tilmanocept (reverse concordance).

In one Phase 3 clinical study in patients with intraoral or cutaneous squamous cell carcinoma, technetium Tc 99m tilmanocept localised sentinel lymph nodes in 97.59% of patients who underwent lymph node evaluation. Relative to the pathology status of lymph node collection from a complete lymph node dissection, technetium Tc 99m tilmanocept correctly localised in sentinel lymph nodes predictive of harbouring metastatic tumour in 38 of 39 patients, for a false negative rate of 2.56%. The overall accuracy of technetium Tc 99m tilmanocept for identification of true positive and true negative patients relative to pathology in the localised lymph nodes was 98.80%.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Lymphoseek in one or more subsets of the paediatric population for visualisation of lymphatic drainage of solid malignant tumours for diagnostic purposes (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Two Phase 1 clinical trials in breast cancer patients and one Phase 1 study in melanoma patients have been completed. The purpose of the studies included the radiopharmacokinetic evaluation of Lymphoseek.

Distribution

In one Phase 1 study in breast cancer patients, Lymphoseek at all three doses tested (4, 20, and 100 micrograms) exhibited fast injection site clearance (elimination rate constants in the range of 0.222/h to 0.278/h). Uptake of technetium Tc 99m tilmanocept into the primary sentinel node increased dose-dependently ($p=0.009$): Lymphoseek injection at 4, 20, and 100 micrograms produced primary sentinel node levels (L_{SN}) of 0.09 ± 0.20 pmol, 6.53 ± 2.52 pmol, and 10.58 ± 8.43 pmol of technetium Tc 99m

tilmanocept, respectively. The percent-of-injected dose reaching the primary sentinel node ($\%ID_{SN}$) was 0.05% ± 0.10%, 0.52% ± 0.38%, 0.21% ± 0.17% in the 4, 20, and 100 microgram Lymphoseek dose groups, respectively. The plasma %ID per gram for two dose levels peaked at 4 hours; the mean values for the 4 and 100 microgram doses were 0.0090%/g ± 0.0048%/g and 0.0039%/g ± 0.0046%/g, respectively. The 20 microgram dose peaked at 2.5 hours with a mean %ID/g of 0.0023%/g ± 0.0005%/g.

In the second Phase 1 study in breast cancer patients in which patients were injected with 20 micrograms Lymphoseek, the mean elimination rate constant of technetium Tc 99m tilmanocept was 0.299/h and the drug half-life at the injection site was 2.6 h. The $\%ID_{SN}$ was 1.68% ± 1.22% in the 3 hour injection-to-surgery group and 1.81% ± 2.19% in the Lymphoseek 16 hour injection-to-surgery group.

In the Phase 1 study in melanoma patients, Lymphoseek at all three doses tested (20, 100, and 200 micrograms) cleared the injection site with elimination rate constants in the range of 0.227/h to 0.396/h, resulting in drug half-life at the injection site of 1.75 to 3.05 h). Uptake of technetium Tc 99m tilmanocept into the primary sentinel node increased dose-dependently: Lymphoseek injection at 20, 100, and 200 micrograms produced L_{SN} values of 5.01 ± 8.02 pmol, 17.5 ± 13.7 pmol, and 58.2 ± 41.2 pmol of technetium Tc 99m tilmanocept, respectively. The $\%ID_{SN}$ taken up into the primary lymph node was 0.50% for the 20 microgram dose, 0.35% for the 100 microgram dose, 0.58% for the 200 microgram dose of Lymphoseek. The plasma %ID per gram for two dose levels peaked at 15 minutes; the mean values for the 20 and 200 microgram doses were 0.0104%/g ± 0.0135%/g and 0.0065%/g ± 0.0082%/g, respectively. The 100 microgram dose peaked at 1 and 2 hours with a mean %ID/g of 0.0018%/g ± 0.001%/g at each timepoint.

Elimination

Technetium Tc 99m tilmanocept is eliminated primarily through the kidneys. The metabolism of technetium Tc 99m tilmanocept has not been investigated experimentally. Tilmanocept may be metabolised in the liver to its component molecules, namely dextran (which is renally excreted and/or further metabolised to glucose), mannose (an endogenous sugar) and diethylenetriaminepentaacetic acid (which is renally excreted). As with all general metabolites, especially those in which the liver plays a measurable roll of elimination, some biliary elimination of technetium Tc 99m tilmanocept is also likely to occur.

The %ID for liver, kidneys, and bladder as calculated from the whole body scans of breast cancer patients at 1, 2.5, and 12 hours after administration was below 2.6% at all times (all dose levels combined). The %ID for liver, kidneys, and bladder as calculated from the whole body scans of melanoma patients at 1 and 12 hours after administration ranged from 1.1% to 3.1% at 1 hour, and all decreased to less than 1% by 12 hours.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity, and genotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trehalose dihydrate
Glycine (E640)
Sodium ascorbate (E301)
Stannous chloride dihydrate (E512)
Sodium hydroxide (E524)
Hydrochloric acid, dilute (E507)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6 and 12.

6.3 Shelf life

Unopened vial
18 months.

After radiolabelling
6 hours. Do not store above 25°C. Store using appropriate radiation shielding.

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

Do not store above 25°C.
Store the vial in the outer carton 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

8 mL type I glass vial with a butyl rubber stopper sealed with a flip-off seal. Each vial contains 50 micrograms tilmanocept.

Pack-size of 1 and 5 vials.

6.6 Special precautions for disposal and other handling

General warning
Radiopharmaceuticals should be received, used, and administered only by authorised 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 organisation.

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 vial are intended only for use in the preparation and radiolabelling of Lymphoseek and are not to be administered directly to the patient without first undergoing the preparative procedure. Each 50 microgram vial contains an additional overfill to ensure that 50 micrograms of tilmanocept can be delivered. However, it is required that the vial be prepared as instructed and a 50 microgram aliquot be used for a single patient dose; any remaining material should be discarded after reconstitution and use, see section 12.

For instructions on reconstitution and radiolabelling of the medicinal product before administration, see section 12. The radiolabelled product is a clear, colourless solution with no visible particles.

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

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

The content of the kit before extemporary preparation is not radioactive. However, after sodium

pertechnetate (^{99m}Tc) 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 spill of urine, vomiting, 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

Navidea Biopharmaceuticals Europe Ltd.
Kilminion South
Ballinroad
Dungarvan
Co. Waterford, X35 WP70
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/955/002
EU/1/14/955/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 November 2014
Date of latest renewal: 16 September 2019

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY

Technetium (^{99m}Tc) is produced by means of a (^{99}Mo/^{99m}Tc) generator and decays with the emission of gamma radiation with a mean energy of 140 keV and a half-life of 6.02 hours to technetium (^{99m}Tc) which, in view of its long half-life of 2.13 x 10^5 years can be regarded as quasi stable.

The radiation dose estimation for a number of organs is based on MIRD reference man and MIRD S values, and has been calculated from biological data of organ uptake and blood clearance.

The radiation doses to organs and tissues of an average patient (70 kg) per MBq of radiolabelled Lymphoseek are shown in Table 1 and Table 2.

Table 1. Estimated dose absorbed from Lymphoseek in patients with breast cancer[a]

Estimated radiation absorbed dose for breast cancer, mGy/MBq	
Target organ	**Adults**
brain	0.0002
breast (injection site)	0.0897
gall bladder wall	0.0019
lower large intestine wall	0.0007
small intestine	0.0005
stomach	0.0010

upper large intestine wall	0.0007
kidney	0.0101
liver	0.0018
lungs	0.0020
muscle	0.0005
ovaries	0.0101
red marrow	0.0007
bone	0.0010
spleen	0.0015
testes	0.0027
thymus	0.0063
thyroid	0.0048
urinary bladder	0.0032
total body (blood)[b]	0.0011
Effective dose (E) (males, mSv/MBq)	0.01600
Effective dose (E) (females, mSv/MBq)	0.01785

[a] Calculated from data of 18 breast cancer patients who received four peritumoural injections of 4, 20, and 100 microgram doses of Lymphoseek.

[b] Blood represents total body exposure segregated from independent measurements of other organs and tissues.

Table 2. Estimated dose absorbed from Lymphoseek in patients with melanoma[a]

Estimated radiation absorbed dose for melanoma, mGy/MBq	
Target organ	**Adults with melanoma**
brain	0.0050
breast (injection site)	0.0427
gall bladder wall	0.0038
lower large intestine wall	0.0031
small intestine	0.0032
stomach	0.0030
upper large intestine wall	0.0031
kidney	0.0150
liver	0.0050
lungs	0.0032
muscle	0.0024
ovaries	0.0162
red marrow	0.0027
bone	0.0047
spleen	0.0032
testes	0.0056
thymus	0.0031
thyroid	0.0025
urinary bladder	0.0076
total body (blood)[b]	0.0030
Effective dose (E) (males, mSv/MBq)	0.01094
Effective dose (E) (females, mSv/MBq)	0.01357

[a] Calculated from data of 18 melanoma patients who received four intradermal injections of 20, 100, and 200 microgram doses of Lymphoseek.

[b] Blood represents total body exposure segregated from independent measurements of other organs and tissues.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Radiation safety – Product handling
Use waterproof gloves, effective radiation shielding, and appropriate safety measures when handling Lymphoseek 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 experience 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.

Directions for radiolabelling the tilmanocept powder 50 micrograms vial with technetium Tc 99m general considerations
The vial components of the kit are sterile, non-pyrogenic, and are intended solely for use in the preparation of Lymphoseek. Do not administer the unprepared vial components of the kit directly to a patient. Follow aseptic procedures during preparation and administration.

Follow appropriate radiation safety precautions during preparation and administration. Use radiation shielding for radiolabelled Lymphoseek to prevent radiation exposure.

Use only eluate from technetium Tc 99m generator which was previously eluted within 8 hours. For the highest radiochemical purity, reconstitute with freshly eluted technetium Tc 99m generator eluate.

Technetium Tc 99m labelling reactions depend on maintaining the stannous ion in the reduced state. Sodium pertechnetate (Tc 99m) injection containing oxidants should not be used to reconstitute this kit. Vials are sealed under nitrogen; air or oxygen is harmful to the contents of the vial and therefore the vial should not be vented.

Lymphoseek, radiolabelled solution for injection should be used within 6 hours after reconstitution. The dose must contain no less than the intended level of Tc 99m radioactivity for same day surgery (18.5 MBq) or next day surgery (74 MBq) at the time of administration.

Determination of injection volumes
Lymphoseek may be administered to a patient as a single injection or as multiple injections. Prior to preparation, determine the planned injection technique and the number of injections that will be used for a given patient. For each injection prepare a separate syringe. Based on the planned number of injection syringes and the planned total injection volume per patient, determine (from Table 3 below) the reconstituted vial volume of radiolabelled Lymphoseek.

Each Lymphoseek vial, once reconstituted and radiolabelled, would contain 50 micrograms of product with an additional overfill when prepared according to the instructions and administered as noted in Table 3. The overfill is 12.5 micrograms to allow for radiochemical purity testing and to ensure that 50 micrograms of tilmanocept can be delivered. The total contents of the vial should not be administered to a single patient. The radiolabelled product is to be used within 6 hours of its preparation. Discard unused product.

Table 3: Lymphoseek injections by injection volume

Desired number of injections	Total volume to be injected	Total Lymphoseek vial reconstitution volume
1 x 0.1 mL injection	0.1 mL	0.125 mL
5 x 0.1 mL injections, or 2 x 0.25 mL injections, or 1 x 0.5 mL injection	0.5 mL	0.625 mL
5 x 0.2 mL injections, or 4 x 0.25 mL injections, or 2 x 0.5 mL injections	1.0 mL	1.25 mL

Method of preparation

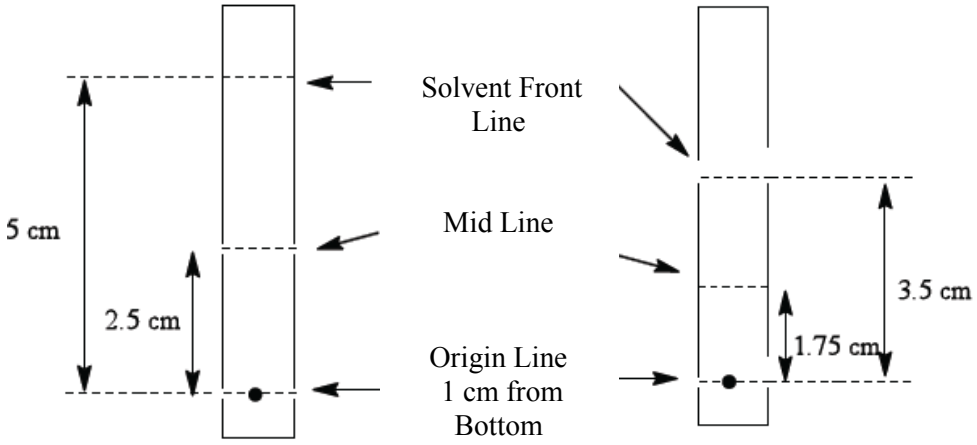
Preparation of the Lymphoseek radiolabelled solution for injection from the kit is done by the following aseptic procedure:

a. Prior to radiolabelling, inspect the tilmanocept powder vial for any damage. Do not use if vial integrity appears compromised.
b. For radiolabelling, use sodium pertechnetate (Tc 99m) solution from a technetium Tc 99m generator within 8 hours of its elution.
c. Do not vent the tilmanocept powder vial prior to or during radiolabelling.
d. Using a sterile syringe, aseptically draw approximately 23.1 MBq or 92.5 MBq of sodium pertechnetate (Tc 99m) solution in either about 0.125 mL volume (for 0.125 mL reconstituted vial volume) or about 0.5 mL volume (for 0.625 mL or 1.25 mL reconstituted vial volume). Assay the syringe for technetium Tc 99m activity in a dose calibrator.
e. Prior to radiolabelling, write the radioactivity amount, the reconstituted vial volume, date and time, expiration time and lot number in the space provided on the radioactive product vial label and affix it to the tilmanocept powder vial. Place the vial in a radiation shield and sanitize the septum with an alcohol wipe.
f. Aseptically add sodium pertechnetate (Tc 99m) solution (from step d above) to the tilmanocept powder vial. Without withdrawing the needle, remove an equal volume of headspace gas. Do not vent.
g. Remove the needle, gently swirl the vial to mix the contents, and then let it stand at room temperature for at least 15 minutes.
h. Aseptically add sterile sodium chloride 9 mg/mL (0.9%) solution for injection, if needed, to the radiolabelled product in the tilmanocept powder vial to bring the volume to the reconstituted vial volume of 0.125 mL, 0.625 mL, or 1.25 mL prior to filling the patient dose in syringe(s). To normalize pressure, withdraw an equal volume of headspace gas.
i. Assay the radiolabelled vial for total radioactivity using a dose calibrator. Write the technetium Tc 99m activity concentration, total volume, assay time and date, expiration time, and lot number on the shield label supplied with the kit. Affix the label to the shield.
j. Determine the radiochemical purity of the radiolabelled product as described below.
k. Withdraw the required volume of the radiolabelled product into the required number of syringes. Assay the syringe(s) in a dose calibrator. Write the radioactivity amount, date and time of assay, volume, and expiration time (this is not to exceed 6 hours from preparation time) on a syringe label and affix it to the syringe(s).
l. Store the radiolabelled product in a shield. Do not store above 25°C. Use within the expiry time on the label.

Determination of radiochemical purity of radiolabelled Lymphoseek

Determine radiochemical purity of the radiolabelled Lymphoseek by Instant Thin Layer Chromatography (ITLC) using either Whatman Grade 1, 3MM, 31ET Chr or Biodex 150-001 Red Strips (cellulose chromatography paper) using the following method:

a. Mark the chromatographic strip for origin, mid and solvent front lines with a pencil as shown below:



Whatman Grade 1, 3MM, 31ET Chromatography strip

Biodex 150-001 Red Strips

b. Apply a small drop (3 - 10 microliters) of the radiolabelled product at the center of the origin line chromatography strip.
c. Place the strip into a chromatography chamber containing 1 mL of acetone as the developing solvent. Allow the solvent to migrate to the solvent front line (5 cm from the bottom of the Whatman strips and 3.5 cm for the Biodex strip). Remove the strip from the chamber, let it dry and cut it in half. Count each half of the strip with a suitable radioactivity counting apparatus (dose calibrator or multichannel analyzer).
d. Calculate the percent radiochemical purity (% RCP) as follows:

$$\% \text{ RCP} = \frac{\text{Counts (activity) in bottom half}}{\text{Counts(activity) in bottom half} + \text{Counts(activity) in top half}} \times 100$$

e. Do not use the radiolabelled Lymphoseek if the radiochemical purity is less than 90%.

Image acquisition/sentinel lymph node mapping

Breast cancer, melanoma, and squamous cell carcinoma of the oral cavity applications in adults:

- In clinical studies, patients received Lymphoseek up to 30 hours before surgery. A handheld gamma counter (represented by any handheld gamma detection probe) was used intraoperatively to identify sentinel lymph nodes localising technetium Tc 99m. In clinical studies using Lymphoseek, study investigators employed a threshold rule for positive localisation of technetium Tc 99m that was estimated using the background radioactivity counts plus three standard deviations from the mean background count level (i.e., the *three-sigma rule*, representing >99.7% probable difference from background) [see Table 4]. Background counts were typically determined from tissue at least 20 centimetres distal to the injection site.

Table 4: Example of three-sigma rule threshold

Background count[a]	Three-sigma threshold value
5	11.71
10	19.49
15	26.62
20	33.42
25	40.00

[a] Average of three 2-second counts or one 10-second count

- All lymphatic mapping agents use elements of the lymphatic system for distribution. The imaging and detection of sentinel lymph nodes with Lymphoseek is dependent upon its specific molecular targeting and binding to reticuloendothelial cells within lymph nodes. Distortion of the underlying lymphatic

system architecture and function by prior extensive surgery, radiation, or metastatic disease may result in diminished Lymphoseek localisation in lymph nodes. Based on clinical studies, the rate of localisation (percent of all patients with at least one hot node) and degree of localisation (average number of hot nodes per patient) of Lymphoseek is not dependent on the radiopharmaceutical injection technique. The use of Lymphoseek is intended to complement palpation, visual inspection, and other procedures important to lymph node localisation. Intraoperative lymphatic mapping by gamma detection may begin as early as 15 minutes post-injection and within 30 hours (for next day surgery) of administration of Lymphoseek.

- After injection of Lymphoseek, external gamma detection imaging may be conducted. Recommended time for preoperative imaging is 15 minutes post-injection but may begin as early as 10 minutes. Effective preoperative imaging procedures include planar gamma camera scintigraphy, SPECT, and SPECT/CT. Although these are complementary to intraoperative gamma probing, such acquired images should not be considered a substitute for proficient and thorough intraoperative probing with a handheld gamma detection probe.

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(S) 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(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

GiPharma S.r.l.
Strada Crescentino snc – 13040
Saluggia (VC)
Italia

Norgine B.V.
Antonio Vivaldistraat 150
1083 HP Amsterdam
Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 (PSURs)**

The requirements for submission of PSURs 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.

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

- **Risk management plan (RMP)**

The marketing authorisation holder (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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Lymphoseek 50 micrograms kit for radiopharmaceutical preparation
tilmanocept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 50 micrograms of tilmanocept.

3. LIST OF EXCIPIENTS

Excipients:
Trehalose, dihydrate
Glycine (E640)
Sodium ascorbate (E301)
Stannous chloride, dihydrate
Sodium hydroxide (E524)
Hydrochloric acid, dilute (E507)

4. PHARMACEUTICAL FORM AND CONTENTS

Kit for radiopharmaceutical preparation
1 vial
5 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Instructions for the reconstitution and radiolabelling of the product are included in this pack.
For injection after radiolabelling.
Intradermal, subcutaneous, intratumoural, or peritumoural use after radiolabelling with sodium pertechnetate (^{99m}Tc).

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

8. EXPIRY DATE

EXP:

The radiolabelled solution can be used for 6 hours when stored below 25°C.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

Store the vial in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Navidea Biopharmaceuticals Europe Ltd.
Kilminion South
Ballinroad
Dungarvan
Co. Waterford, X35 WP70
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/955/002 1 vial
EU/1/14/955/001 5 vials

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

Vial label

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

Lymphoseek 50 micrograms kit for radiopharmaceutical preparation
tilmanocept

2. METHOD OF ADMINISTRATION

For injection after radiolabelling with sodium pertechnetate (^{99m}Tc).

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Contains an overfill.

Navidea

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

Lymphoseek 50 micrograms solution for injection
technetium (^{99m}Tc) tilmanocept

Intradermal, subcutaneous, intratumoural, or peritumoural use.

2. METHOD OF ADMINISTRATION

For injection

3. EXPIRY DATE

Use within 6 hours of 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

Contains an overfill.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Lymphoseek 50 micrograms kit for radiopharmaceutical preparation
tilmanocept

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 Lymphoseek is and what it is used for

This medicine is for diagnostic use in adults only. This means that it is used in breast cancer, melanoma or oral cavity cancers to help find out about your illness. It is not a treatment for your illness.

Before it is used, the powder in the vial which contains tilmanocept is mixed with a radioactive medicine called sodium pertechnetate (containing ^{99m}Tc) to make a substance called technetium (^{99m}Tc) tilmanocept.

Since technetium (^{99m}Tc) tilmanocept contains a small amount of radioactivity it can make parts of the body areas visible to doctors during tests to help them see if the cancer has spread to places called 'lymph nodes' that are found near tumours. The lymph nodes nearest the tumour are called 'sentinel' lymph nodes. These lymph nodes are where cancer cells are most likely to have spread. When Lymphoseek has found the sentinel lymph nodes, they can be removed and checked to see if there are any cancer cells present. Lymphoseek finds the lymph nodes and can be detected using a special camera or detector.

The use of Lymphoseek does involve exposure to small amounts of radioactivity. Your doctor and the nuclear medicine doctor have considered that the clinical benefit that you will obtain from the procedure with the radiopharmaceutical outweighs the risk due to radiation.

2. What you need to know before Lymphoseek is used

Do not use Lymphoseek
If you are allergic to tilmanocept or any of the other ingredients of this medicine (listed in section 6) or to any of the ingredients of the radiolabelled pharmaceutical.

Warnings and precautions
Talk to your nuclear medicine doctor before you are given Lymphoseek:

- if you have experienced any signs of allergic reaction (listed in section 4) after previous admistration of Lymphoseek
- if you have kidney or liver problems (renal or heptatic disease)

Children and adolescents
This medicine is not for use in children and adolescents under 18 years of age because it has not been studied in this age group.

Other medicines and Lymphoseek
Tell your nuclear medicine doctor if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines.

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 Lymphoseek 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.

If you are pregnant, the nuclear medicine doctor will only administer this product during pregnancy if a benefit is expected which would outweigh the risks.

If you are breast-feeding, breast milk should be discarded for 24 hours after administration of Lymphoseek. Please ask your nuclear medicine doctor when you can resume breast-feeding.

Driving and using machines
It is considered unlikely that Lymphoseek will affect your ability to drive or to use machines. Your doctor and nuclear medicine doctor will tell you when it is safe to drive after your surgery.

Lymphoseek contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose. That means it is essentially 'sodium-free'.

3. How to use Lymphoseek

This medicine is for hospital use only.

There are strict laws on the use, handling and disposal of radiopharmaceutical products. Lymphoseek will only be used in special controlled areas. This product will only be handled and given to you by people who are trained to use it safely. These people 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 the quantity of Lymphoseek 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 18.5 to 74 MBq (megabecquerel, the unit used to express radioactivity).

The dose may be divided up into smaller amounts. This means that the doctor can make more than one injection in the area around the tumour.

Before administration of Lymphoseek you should:
Follow the instructions of your doctor or nuclear medicine doctor.

Administration of Lymphoseek and conduct of the procedure
Lymphoseek is injected under the skin, under the nipple, or in or around the tumour. The place depends on the type of tumour.

Lymphoseek is given either the day before or on the day of your procedure.

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

The nuclear medicine doctor uses a special camera to find Lymphoseek. The surgeon uses the pictures taken to see where the sentinel lymph nodes are located. The surgeon will also use a machine that finds the ^{99m}Tc part of the medicine. The ^{99m}Tc shows the surgeon where the sentinel lymph nodes are located.

When the sentinel lymph node is found, the surgeon removes it. If there is more than one sentinel lymph node, they will remove these nodes as well. The sentinel lymph nodes are then checked to see if cancer cells have spread to them.

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

If you have been given more Lymphoseek than you should
An overdose is unlikely because you will get a specially measured amount of Lymphoseek precisely controlled by the doctor supervising the procedure. However, in the case of an overdose, you will receive the appropriate treatment.

If you have any further questions on the use of this medicine, 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. The following side effects may happen with this medicine:

Uncommon (may affect up to 1 in 100 people):
- irritation or pain where the injection is given (including the breast and skin)
- wound pain, wound opening or accumulation of fluid at surgical site
- feeling sick (nausea) or dizzy
- blurred vision
- difficulty speaking
- headache
- increased heart rate
- frequent or urgent need to urinate
- feeling of warmth, a pricking or tingling sensation, or pain in an extremity, shoulder, the neck or jaw
- flushing
- high levels of calcium in the blood

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 doctor or nurse. 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 to store Lymphoseek

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.

Do not use this medicine after the expiry date which is stated on the carton and label after "Exp". The expiry date refers to the last day of that month.

Do not store above 25°C. Store the vial in the outer carton in order to protect from light.

The radiolabelled solution is stable for 6 hours at a maximum of 25°C.

The radiolabelled product is a clear, colourless solution with no visible particles. Do not use if particulate matter and/or discoloration are seen.

Disposal of radiopharmaceuticals should be done in accordance with national regulation on radioactive materials. These measures will help protect the environment.

6. Contents of the pack and other information

What Lymphoseek contains

- The active substance is tilmanocept. Each vial contains 50 micrograms of tilmanocept.
- The other ingredients are trehalose, dihydrate, glycine (E640), sodium ascorbate (E301), stannous chloride, dihydrate, sodium hydroxide (E524) and hydrochloric acid, dilute (E507).

What Lymphoseek looks like and contents of the pack
Before it is used, the powder in the vial is mixed with another medicine called sodium pertechnetate to make a substance called technetium (^{99m}Tc) tilmanocept.

Pack sizes
The glass vials are supplied in a carton containing 1 or 5 vials.

Marketing Authorisation Holder
Navidea Biopharmaceuticals Europe Ltd.
Kilminion South
Ballinroad
Dungarvan
Co. Waterford, X35 WP70
Ireland

Manufacturer
GiPharma S.r.l.
Strada Crescentino snc – 13040
Saluggia (VC)
Italia

Norgine B.V.
Antonio Vivaldistraat 150
1083 HP Amsterdam
Netherlands

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 Lymphoseek is provided as a tear-off section at the end of the printed leaflet 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 [SmPC should be included in the box].