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

RoTecPSMA 80 micrograms kit for radiopharmaceutical preparation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The kit contains two different vials: Vial 1 and Vial 2.

Vial 1 contains 80 micrograms of trofolastat.

Vial 2 contains 0.75 ml 0.35 M hydrochloric acid solution.

The radionuclide is not part of the kit.

Excipient with known effect

Each kit contains 5.17 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.

Vial 1: white to off-white powder

Vial 2: clear, colourless solution with a pH $\leq$ 1.0

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

RoTecPSMA, after radiolabelling with sodium pertechnetate (^{99m}Tc) solution, is indicated for the detection of prostate specific membrane antigen (PSMA)-positive lesions with single photon emission computed tomography (SPECT) in adults with prostate cancer (PCa) in the following clinical settings:

- Primary staging of patients with high-risk PCa prior to primary curative therapy,
- Suspected PCa recurrence in patients with increasing levels of serum prostate-specific antigen (PSA) after primary curative therapy,
- Selection of patients with metastatic PCa for whom PSMA-targeted therapy is indicated.

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 to be given to adults is 740 ± 111 MBq for planar scintigraphy and for SPECT studies.

Elderly population

No special dosage regimen for elderly patients is required.

Paediatric population

There is no relevant use of RoTecPSMA in the paediatric population for the identification of PSMA-positive lesions in prostate cancer.

Hepatic impairment / Renal impairment

The safety and efficacy of technetium (^{99m}Tc) trofolastat have not been studied in patients with hepatic impairment or renal impairment. Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients, see section 4.4.

Method of administration

This medicinal product should be radiolabelled before administration to the patient.

Technetium (^{99m}Tc) trofolastat is administered intravenously as a single injection.

A dose of 740 ± 111 MBq technetium (^{99m}Tc) trofolastat solution will be administered.

For instructions on radiolabelling of the medicinal product before administration, see section 12.

For patient preparation, see section 4.4.

Image acquisition

Technetium (^{99m}Tc) trofolastat is suitable for SPECT medical imaging.

Patients should void immediately prior to image acquisition. The patient should be positioned supine with the arms above the head, as tolerated by the patient. A CT scan should be obtained for attenuation correction and anatomical correlation. The acquisition should include a whole-body acquisition from the base of the skull to mid-thigh.

The recommended time for SPECT imaging is 3 to 6 hours after injection of technetium (^{99m}Tc) trofolastat solution. 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 or 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

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 or hepatic impairment

The safety and efficacy of technetium (^{99m}Tc) trofolastat have not been studied in patients with renal or hepatic impairment. Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.

Paediatric population

For information on use in the paediatric population, see section 4.2.

Patient preparation

There is no need for fasting. Patients are allowed to take all their medications. PSMA-expression may be increased by androgen-deprivation therapy, but the clinical significance is unclear.

The patient must be well-hydrated before technetium (^{99m}Tc) trofolastat administration and must void just prior to the image acquisition. The patient should be urged to void as often as possible during the first hours after the examination in order to reduce radiation.

Interpretation of technetium (^{99m}Tc) trofolastat images

Technetium (^{99m}Tc) trofolastat binds to PSMA on the surface of PSMA-expressing cells. Based on the intensity of the signals, SPECT images obtained with technetium (^{99m}Tc) trofolastat indicate the presence of PSMA protein in tissues.

Technetium (^{99m}Tc) trofolastat images should be interpreted by appropriately trained personnel.

While the uptake of technetium (^{99m}Tc) trofolastat reflects the levels of PSMA expression in prostate cancer, technetium (^{99m}Tc) trofolastat uptake is not specific to prostate cancer and may occur in other types of cancers, non-malignant processes and normal tissues.

Clinical correlation, which may include histopathological evaluation of the suspected prostate cancer site, is recommended. A negative image does not rule out the presence of prostate cancer and a positive image does not confirm the presence of prostate cancer.

Small lymph node metastases, or any lesion (<5 mm) may be missed by technetium (^{99m}Tc) trofolastat SPECT/CT due to spatial resolution of SPECT.

The performance of technetium (^{99m}Tc) trofolastat for imaging of patients with biochemical evidence of recurrence of prostate cancer seems to be affected by serum PSA levels (see section 5.1).

Limitations of use

Prostate cancer lesions which do not bear PSMA receptors will not be visualized.

After the procedure

Patient should be encouraged to remain well hydrated and void as often as possible during the first hours after the scan in order to reduce radiation exposure of the bladder.

Close contact with infants and pregnant women should be avoided during the first twelve (12) hours after administration of the radiopharmaceutical.

Specific warnings

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, 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

No interaction studies have been performed.

Androgen deprivation therapy (ADT) and other therapies targeting the androgen pathway, such as androgen receptor antagonists, may result in changes in uptake of technetium (^{99m}Tc) trofolastat in prostate cancer. The effect of these therapies on performance of technetium (^{99m}Tc) trofolastat has not been established.

4.6 Fertility, pregnancy and lactation

Technetium (^{99m}Tc) trofolastat is not indicated for use in women.

Fertility

No studies on fertility have been performed.

4.7 Effects on ability to drive and use machines

RoTecPSMA has no known influence on the ability to drive and use machines.

4.8 Undesirable effects

The safety of technetium (^{99m}Tc) trofolastat was evaluated in a total of seven prospective clinical studies. No significant safety findings have been reported. No serious adverse events have been reported and no deaths or withdrawals due to safety concerns have occurred in any of the studies.

Adverse reactions were reported during clinical studies are listed below with corresponding frequency categories. 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)
Not known	(cannot be estimated from the available data)

System Organ Class	**Frequency**	**Adverse reaction**
Nervous system disorders	Common	Headache
	Uncommon	Dizziness
	Uncommon	Dysgeusia
	Uncommon	Paraesthesia
	Uncommon	Presyncope
	Uncommon	Somnolence
	Uncommon	Tension headache
General disorders and administration site conditions	Uncommon	Fatigue
	Uncommon	Influenza like illness
	Uncommon	Injection site extravasation
	Uncommon	Oedema peripheral

Vascular disorders	Uncommon	Hypertension
	Uncommon	Flushing
	Uncommon	Hot flush
	Uncommon	Orthostatic hypotension
Gastrointestinal disorders	Uncommon	Nausea
	Uncommon	Abdominal discomfort
	Uncommon	Toothache
Investigations	Uncommon	Aspartate aminotransferase increased
	Uncommon	Blood bilirubin increased
	Uncommon	Blood pressure increased
Eye disorders	Uncommon	Eye irritation
	Uncommon	Vitreous floaters
Immune system disorders	Uncommon	Drug hypersensitivity
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia
	Uncommon	Neck pain
Renal and urinary disorders	Uncommon	Chromaturia

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 6.5 mSv when the recommended activity of 740 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the event of administration of a radiation overdose with technetium (^{99m}Tc) trofolastat the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition and defecation. It might be helpful to estimate the effective dose that was applied.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals for tumour detection, technetium (^{99m}Tc) compounds, ATC code: V09IA10

Mechanism of action

Technetium (^{99m}Tc) trofolastat is a technetium-99m labelled small molecule with high affinity binding to the extracellular domain of prostate-specific membrane antigen (PSMA). PSMA is expressed on nearly all prostate cancers resulting in the ability to detect and localize prostate cancer in the prostate gland, pelvic lymph nodes and/or metastatic lesions throughout the body.

Pharmacodynamic effects

At concentrations used for diagnostic examination, no pharmacodynamic activity is expected for technetium (^{99m}Tc) trofolastat.

Clinical efficacy

Primary staging of patients with high-risk prostate cancer (PCa) prior to primary curative therapy

Efficacy data for primary staging of patients with high-risk PCa derives from study MIP-1404-201. In this multicentre, multireader prospective study efficacy of technetium (^{99m}Tc) trofolastat for detection of prostate gland and pelvic lymph node (LN) cancer was assessed in 105 patients with histopathology as gold standard. Patients were adult men and diagnosed with intermediate- and high-risk PCa scheduled for radical prostatectomy and extended pelvic LN dissection. Results showed a high detection rate of technetium (^{99m}Tc) trofolastat imaging to correctly identify subjects who had prostate cancer at the gland level (94.2 % sensitivity, 95 % CI 87.8-97.9) as well as correctly assessing evaluable prostate segments which were cancer free (83.3 % specificity, 95 % CI 76.9-88.6) compared to histology. Visual scores and tumour-to-background ratios correlated significantly with Gleason scores. Technetium (^{99m}Tc) trofolastat SPECT/CT detected LN involvement regardless of LN size with a sensitivity of 30 % (95% CI 11.7-54.6) and specificity of 96.4 % (95 % CI 87.5-99.7). Lymph nodes with a size of ≥ 5 mm were detected with a sensitivity of 50 % (95 % CI 20.6-79.4). Comparing imaging modalities, Technetium (^{99m}Tc) trofolastat image assessments had higher overall prostate gland sensitivity and prostate segments specificity compared with standard MRI (93.8 % vs 85.4 %, and 85.5 % vs 78.6 %; respectively).

Suspected prostate cancer (PCa) recurrence in patients with increasing levels of serum prostate-specific antigen (PSA) after primary curative therapy

Efficacy of technetium (^{99m}Tc) trofolastat SPECT/CT in patients with biochemical recurrent PCa was evaluated in three studies; Reinfelder *et al.* 2017 (Clin Nucl Med 2017; 42(1): 26-33), Schmidkonz *et al.* 2018 (Prostate 2018; 78(1): 54-63) and Schmidkonz *et al.* 2019 (Ann Nucl Med 2019; 33(12): 891-898).

Reinfelder and colleagues (Reinfelder *et al.* 2017) detected technetium (^{99m}Tc) trofolastat positive lesions in 42 of 60 (70 %; 95 % CI 58-82) patients with biochemical relapse. Twenty patients had technetium (^{99m}Tc) trofolastat positive lymph nodes suggestive of metastasis, 14 patients had pathological uptake in the prostate region indicative of local recurrence, and for another 19 patients, there was tracer accumulation in the skeleton (n = 18) or lungs (n = 1). Detection rate was 91.4 % (95 % CI 82-100) at prostate-specific antigen (PSA) levels greater than 2 ng/mL and 40.0 % (95 % CI 21-59) at lower PSA values ($P < 0.01$).

Schmidkonz and colleagues (Schmidkonz *et al.* 2018) used technetium (^{99m}Tc) trofolastat imaging in workup of 225 PCa patients with biochemical recurrence. Whole-body planar and SPECT/CT images of the lower abdomen and thorax were obtained and analysed for presence and location of abnormal uptake. Technetium (^{99m}Tc) trofolastat positive lesions were detected in 77 % (174/225) of all patients. Detections occurred at the area of local recurrence in the prostate in 25% (n = 56) of patients, with metastases in lymph nodes in 47 % (n = 105), bone in 27 % (n = 60), lung in 5 % (n = 12), and other locations in 2 % (n = 4) of patients. Detection rates were 90 % at PSA levels ≥2 ng/mL, 62 % at PSA levels of 1-3 ng/ml and 58 % at levels of 1 ng/ml or less.

In their second study Schmidkonz and colleagues (Schmidkonz *et al.* 2019) investigated the performance of technetium (^{99m}Tc) trofolastat SPECT/CT in patients with biochemical recurrence of prostate cancer presenting with PSA serum levels below 1 ng/mL. Technetium (^{99m}Tc) trofolastat scans of 50 patients (25 with PSA levels between > 0.5 and 1 ng/mL and 25 with PSA levels between 0.2 and 0.5 ng/mL) that had undergone whole-body planar scintigraphy and SPECT/CT of the thorax, abdomen and pelvis, were analysed. Pathological uptake suggestive of tumour recurrence was detected in 44 % of patients with PSA between 0.2 and 0.5 ng/mL and in 56 % of patients with PSA between > 0.5 and 1 ng/mL. Gleason scores ≥ 8 and the presence of antiandrogen deprivation therapy were further significant predictors of pathological technetium (^{99m}Tc) trofolastat uptake.

Technetium (^{99m}Tc) trofolastat SPECT/CT detection rates per PSA range in PCa patients with biochemical recurrence are summarised in the table below.

Schmidkonz *et al.* 2019 (Ann Nucl Med 2019; 33(12): 891-898)	**Schmidkonz *et al.* 2018 (Prostate 2018; 78(1): 54-63)**	**Reinfelder *et al.* 2017 (Clin Nucl Med 2017; 42(1): 26-33)**
PSA 0.2 - 0.5 ng/mL 44 % (95 % CI 24-65)	PSA ≤ 1 ng/mL 58 % (95 % CI 42-73)	PSA ≤ 1 ng/mL 36.4 % (95 % CI 8-65)
PSA >0.5 - 1 ng/mL 56 % (95 % CI 35-76)	PSA 1 - 3 ng/mL 62 % (95% CI 49-74)	PSA 1 - 3 ng/mL 74.4 % (95 % CI 26-69)
	PSA ≥ 2.0 ng/mL 90 % (95 % CI 85-95)	PSA > 2.0 ng/mL 91.4 % (95 % CI 82-100)

Selection of patients with metastatic prostate cancer (PCa) for whom PSMA-targeted therapy is indicated

Efficacy data for selection of patients with metastatic PCa for whom PSMA-targeted therapy derives from two studies.

Cook and colleagues (Cook *et al.* J Nucl Med 2023; 64(2): 227-231) compared ^{68}Ga-PSMA-11 and technetium (^{99m}Tc) trofolastat as companion diagnostic tracer for eligibility for ^{177}Lu-PSMA therapy. For analysis, two cohorts of patients with metastatic castration-resistant PCa (mCRPC) matched for age, prostate-specific antigen level, and total Gleason score, with either technetium (^{99m}Tc) trofolastat SPECT/CT (n = 25) or ^{68}Ga-PSMA-11 PET/CT (n = 25) scans were included in the study. Up to three lesions in each site (prostate/prostate bed, lymph nodes, bone and soft-tissue metastases) as well as normal liver, parotid gland, spleen, and mediastinal blood-pool SUV_{max} were measured. The study data showed that technetium (^{99m}Tc) trofolastat SPECT lesion SUV_{max} was not significantly different from ^{68}Ga-PSMA-11 PET (median, 18.2 vs. 17.3; *P* = 0.93). However, technetium (^{99m}Tc) trofolastat liver SUV_{max} was higher (median, 8.5 vs. 5.8; *P* = 0.002) and lesion-to-liver ratios were lower (median, 2.7 vs. 3.5; *P* = 0.009). There was no significant difference in parotid gland or splenic SUV_{max} or lesion-to-parotid gland ratios between the two tracers.

Derlin and colleagues (Derlin *et al*. J Nucl Med 2025; Epub ahead of print) determined the feasibility, diagnostic performance, and predictive value of technetium (^{99m}Tc) trofolastat SPECT in patients undergoing baseline staging and assessment of eligibility for PSMA targeted therapy for metastatic castration-resistant PCa. Data of 46 patients undergoing technetium (^{99m}Tc) trofolastat planar scintigraphy and SPECT/CT were analysed. Overall image quality was assessed, and images were visually analysed for the presence and localization of pathologic uptake. Technetium (^{99m}Tc) trofolastat findings were compared with the results of post-therapeutic ^{177}Lu-PSMA scans in patients subsequently commencing radioligand therapy (n = 35). As a result, the image quality of technetium (^{99m}Tc) trofolastat scans was rated as excellent in 98 % of cases. Imaging was concordant in 206 of 210 localizations, demonstrating almost perfect agreement with ^{177}Lu-PSMA scans (k = 0.957 [95 % CI, 0.916-0.999]). Uptake intensity higher than liver uptake identified responders (*P* = 0.0115) and was associated with prolonged progression-free survival (median, 146 vs. 96 d; hazard ratio for progression, 0.3838 [95 % CI, 0.1721-0.8556]; *P* = 0.0192). In multivariable analysis, technetium (^{99m}Tc) trofolastat uptake higher than in liver emerged as an independent predictor of treatment response (odds ratio, 12.37 [95 % CI, 1.613-203.3]; *P* = 0.0319).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with RoTecPSMA in all subsets of the paediatric population in visualisation of prostate-specific membrane antigen in prostate cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Distribution

Blood level of technetium (^{99m}Tc) trofolastat reaches maximal concentration in plasma 2 minutes following administration and declines rapidly in a biphasic fashion. Two hours post administration, the blood concentration decreases approximately 17-fold compared to the value two minutes post administration. Technetium (^{99m}Tc) trofolastat is rapidly cleared from the vascular compartment and moves into the extravascular space. The distribution half-life (T ½, α) is 0.15 hours.

Organ uptake

Uptake of technetium (^{99m}Tc) trofolastat was evident in the parotid and salivary glands, liver, kidneys, and gastrointestinal tract. At 4 hours post-injection, approximately 93 % of the injected dose of technetium (^{99m}Tc) trofolastat remained in the body, and at 20 hours 84 % of the injected dose.

Elimination

The activity is excreted mainly by the renal route. Technetium (^{99m}Tc) trofolastat is rapidly eliminated from the blood.
The most rapid rate of urinary clearance is observed during the first 4 hours post-injection. Approximately 5 % - 10 % of the injected dose of technetium (^{99m}Tc) trofolastat is present in the urine by 24 hours post-injection. The elimination half-life is 13.2 hours.

5.3 Preclinical safety data

Non-clinical data did not reveal any special hazard for technetium (^{99m}Tc) trofolastat in humans.

Trofolastat was well-tolerated in single-dose and in repeat-dose toxicity studies over 28 days in rats and dogs. No toxicity was observed.

Safety pharmacology studies evaluating the respiratory and central nervous system effects in rats and the cardiovascular response in telemeterized beagle dogs did not show any effects.

No carcinogenicity and reproductive toxicity studies were performed. Technetium (^{99m}Tc) trofolastat is unlikely to have genotoxic activity as demonstrated by genotoxicity studies.

This agent is not intended for regular or continuous administration.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Vial 1:
Disodium boranocarbonate
Disodium tetraborate decahydrate
Tartaric acid
Sodium carbonate anhydrous
Sodium hydroxide

Vial 2:
Hydrochloric acid
Water for Injection

6.2 Incompatibilities

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

6.3 Shelf life

The shelf life of the packaged product is 18 months.

After radiolabelling: 12 hours. Do not store above 25 °C after radiolabelling.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).

For storage conditions after radiolabelling of the medicinal product, see section 6.3.

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

6.5 Nature and contents of container

RoTecPSMA is supplied as multidose kit consisting of two vials labelled as vial 1 and vial 2 which cannot be used separately.

Vial 1: 10 ml nominal capacity, multi-dose glass vial (Type I Ph. Eur.) closed with a bromobutyl rubber stopper and an aluminum cap with flip-off seal containing 80 micrograms of active substance trofolastat.
Vial 2: 2 ml nominal capacity, glass vial (Type I Ph. Eur.) closed with a bromobutyl rubber stopper and an aluminum cap with flip-off seal containing 0.75 ml of 0.35 M hydrochloric acid solution.

Pack size: 1 Kit (vial 1 and vial 2)
2 Kits (Vial 1 and vial 2)
5 Kits (vial 1 and vial 2)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

General warning

After radiolabelling of RoTecPSMA, the common protective measures for radioactive medicinal product must be applied.

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.

The contents of the vials are intended only for use in the preparation of technetium (^{99m}Tc) trofolastat and are not to be administered directly to a patient without first undergoing the preparative procedure.

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 vial is compromised, the product 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 extemporary preparation is not radioactive. However, after sodium pertechnetate (^{99m}Tc) (Ph. Eur.) 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

ROTOP Pharmaka GmbH
Bautzner Landstrasse 400
01328 Dresden
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 45925/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/03/2025

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/03/2025

10 DATE OF REVISION OF THE TEXT

20/03/2026

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 (^{99}Tc) which, in view of its long half-life of 2.13×10^5 years can be regarded as quasi stable.

Dosimetry data have been published by Vallabhajosula *et al.* 2014 (J Nucl Med 2014; 55: 1791-1798).
The OLINDA/EXM software was used to estimate radiation-absorbed dose to target organs. The adult male model was used for all patients. The urinary bladder was assumed to be voided regularly at 4.8-h intervals (i.e., 5 times per day). The urinary bladder residence times were computed using OLINDA/EXM implementation of the dynamic bladder model. The small bowel and upper and lower large intestinal residence times were computed using the provided implementation of the ICRP publication 30 gut transit model for the adult male.
The average organ absorbed doses and effective dose of technetium (^{99m}Tc) trofolastat are given in the table below:

Technetium (^{99m}Tc) trofolastat	
Organ	**Dose absorbed per unit activity administered (mGy/MBq)**
Kidneys	0.0733
Salivary glands	0.0524
Spleen	0.0218
Thyroid	0.0195
Liver	0.0161
Upper Large Intestine Wall	0.0161
Urinary Bladder Wall	0.0127
Lower Large Intestine Wall	0.0116
Small Intestine	0.0104
Gallbladder Wall	0.0097
Adrenals	0.0089
Pancreas	0.0084
Osteogenic Cells	0.0084
Lungs	0.0065
Stomach Wall	0.0057
Heart Wall	0.0056
Red Marrow	0.0041
Muscle	0.0035
Thymus	0.0031
Testes	0.0026
Skin	0.0020
Brain	0.0012
Total Body	**0.0045**
Effective Dose equivalent (mSv/MBq)	**0.0125**
Effective Dose (mSv/MBq)	**0.0088**

The effective dose resulting from the administration of 740 MBq for an adult weighing 70 kg is 6.5 mSv. For an administered activity of 740 MBq the typical radiation dose to the critical organ (kidney) is 54.24 mGy.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

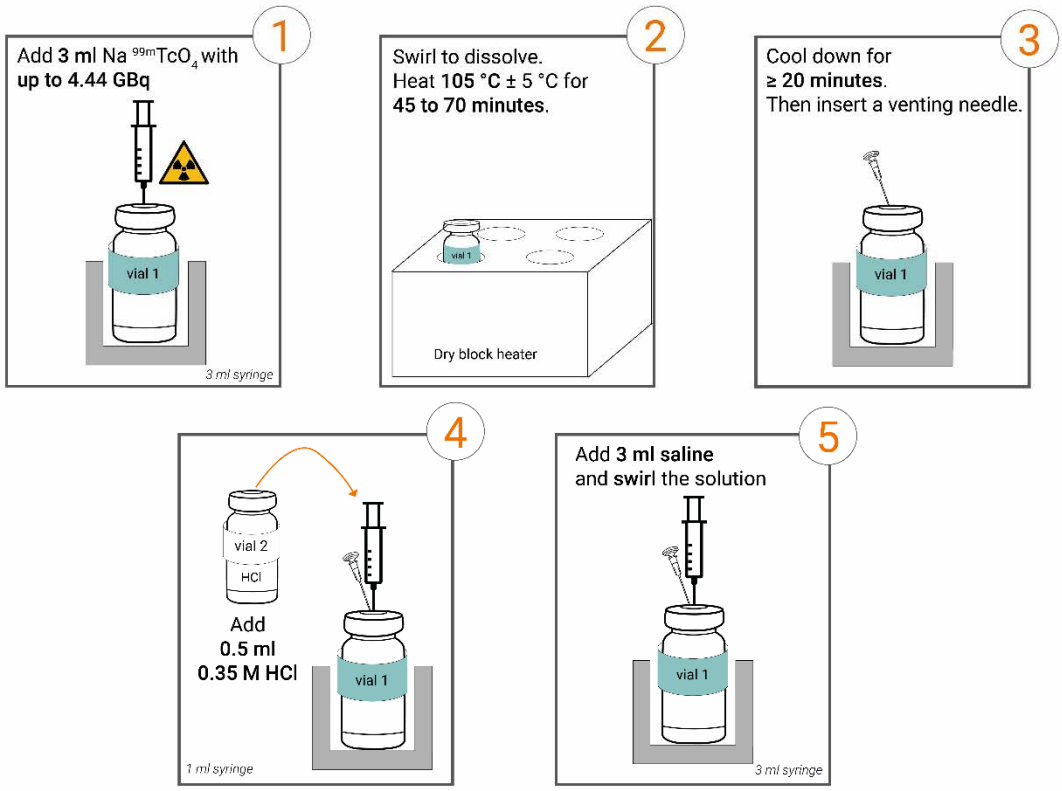
Withdrawals should be performed under aseptic conditions. Usual safety precautions for the handling of radioactive materials should be followed.

The vial must not be opened before disinfecting the stopper, 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.

If the integrity of this vial is compromised, the product should not be used.

Method of preparation

Descriptive process diagram



(1) Set the heating temperature of a block heater at an appropriate temperature to maintain a temperature range of 105 °C ± 5 °C (regular re-calibration is recommended).
(2) Allow vial 1 (containing the lyophilized powder) and vial 2 (hydrochloric acid solution) to adjust to room temperature for at least 15 min. Inspect both vials for any damage. Do not use if vial integrity appears compromised.
(3) Do not vent vial 1 prior to or during heating.
(4) Place vial 1 into an adequate lead shielding. Sanitize the closure of the two vials with a suitable alcohol swap and allow to air dry.
(5) Inject 3 ml of sodium pertechnetate (^{99m}Tc) solution, Ph. Eur., containing up to 4.44 GBq into vial 1. If required, use sterile saline to dilute the sodium pertechnetate (^{99m}Tc) solution to the desired concentration prior to addition to vial 1.
Note: Make sure that the thermometer inserted into the block heater reads 105 ± 5 °C before adding sodium pertechnetate (^{99m}Tc) solution to vial 1.

(6) Swirl vial 1 several times to ensure the product is fully dissolved.
(7) Immediately transfer vial 1 to the block heater. Allow vial 1 to heat for 45 to 70 minutes.
(8) Remove vial 1 from the block heater and place it in an adequate lead shielding. Allow the contents of the vial to cool to room temperature for at least 20 minutes.
(9) Insert a venting needle with suitable sterile filter through the vial stopper. Inject 0.5 ml of 0.35 M hydrochloric acid solution, aseptically drawn from vial 2, and 3 ml of sterile saline. Alternatively, withdraw the same volume of headspace gas from the vial with the same syringe instead of using the venting needle for pressure compensation.

Caution: As the final volume in vial 1 is 6.5 ml, do not insert the venting needle too deep.

(10) Remove the venting needle and mix well by swirling vial 1 several times.
(11) Store vial 1 containing the technetium (^{99m}Tc) trofolastat solution upright in a lead shield container below 25 °C until use.
(12) The radiochemical purity of the technetium (^{99m}Tc) trofolastat solution must be checked. If the radiochemical purity is less than 90 %, the product must not be used.
(13) The technetium (^{99m}Tc) trofolastat solution must be used within twelve (12) hours of time of preparation.

Properties of the product after radiolabelling
Appearance: clear, colourless and without undissolved matter
pH: 5 - 8

Quality Control
Determination of radiochemical purity should be performed using Thin-layer chromatography (TLC).
Both procedures (procedure 1 and procedure 2) given below have to be conducted according to the following instructions.

Chromatographic system:
TLC Plate: Two ITLC-SA strips (use of two chromatographic chambers with cover)
Solvent: Water for injection (WfI) for procedure 1
Methyl ethyl ketone (MEK) for procedure 2
Sample volume: 2 - 3 µl
Start: 1.0 cm from the bottom edge of the plate
Running distance: 5 cm
Detector: Suitable detector

Method:

(1) Depending on the method (both procedures must be performed), fill the chromatographic chambers with the appropiate solvent (WfI or MEK) to a maximum height of 0.5 cm. Then cover the chambers to allow the solvent vapour to equilibrate.
(2) Mark the ITLC-SA strips with a pencil:
- at 1.0 cm from the bottom edge (starting line)
- at 2.5 cm from the bottom edge (integration border/cutting position)
- at 5 cm from the starting line (end of running distance)

(3) Apply one drop (approx. 2 - 3 µl) of the sample solution in the center of the starting line.
Note: The sample volume should be chosen so as to obtain a small spot of maximum 5 mm on the plate. The detection limit of the instrument and thus the minimum activity of the drop of sample solution should also be taken into account.

(4) Place one ITLC-SA strip in each chamber. Place the strips upright and ensure that the spots of the sample are above the solvent surface. Cover the chambers.
(5) Wait until the solvent fronts reach the marked lines (end of the running distances). Remove strips from the chambers and allow to dry.

TLC Procedure 1: Determination of ^{99m}Tc in colloidal form (impurity A)

Solvent: WfI

R_f values:

Chemical compound	**R_f**
Colloidal ^{99m}Tc (**Impurity A**)	0.0 - 0.2
[^{99m}Tc]pertechnetate + [^{99m}Tc]trofolastat	0.8 - 1.0

The technetium (^{99m}Tc, impurity A) in colloidal form remains at the starting point.

TLC Procedure 2: Determination of the [^{99m}Tc]pertechnetate (impurity B) and other hydrophilic impurities (impurity C)

Solvent: MEK

R_f values:

Chemical compound	**R_f**
Colloidal ^{99m}Tc + [^{99m}Tc]trofolastat	0.0 - 0.2
Hydrophilic impurities (**Impurity C**)	0.2 - 0.8
[^{99m}Tc]pertechnetate (**Impurity B**)	0.8 - 1.0

[^{99m}Tc]pertechnetate (impurity B) and hydrophilic impurities (impurity C) move with the eluent front according to the R_f values in the table.

Calculation:

Detection by radio-TLC scanner
The activity distribution is measured and plotted as a chromatogram. Calculate the percentages of the individual peaks.

Detection by radio activity counters without special resolution
Cut the strips at 2.5 cm above their bottom edge. Measure the activity of each part. Relate activity of the pieces to the total activity of each strip and calculate the percentages of the impurities.

Procedure 1:

$$\text{Impurity A [\%]} = \frac{\text{Activity of the lower section}}{\text{Total activity of the strip}} \times 100\ \%$$

Procedure 2:

$$\text{Impurity B [\%]} + \text{C [\%]} = \frac{\text{Activity of the upper section}}{\text{Total activity of the strip}} \times 100\ \%$$

Radiochemical purity (RCP):

$$\text{RCP [\%]} = 100\ \% - (\text{impurity A[\%]} + \text{impurity B [\%]} + \text{C [\%]})$$

If the radiochemical purity of the product is less than 90 %, the product must not be used.