swissmedic

Date: 31 March 2026
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

RoTecPSMA

International non-proprietary name: trofolastat

Pharmaceutical form:	kit for radiopharmaceutical preparation
Dosage strength(s):	80 µg
Route(s) of administration:	intravenous use
Marketing authorisation holder:	medeo AG
Marketing authorisation no.:	69451
Decision and decision date:	approved on 8 August 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, definitions, abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
EAU-EANM	European Association of Urology – European Association of Nuclear Medicine
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PET	Positron emission tomography
PET/CT	Positron emission tomography / computed tomography
PET/MRI	Positron emission tomography / magnetic resonance imaging
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
PSP	Pediatric study plan (US FDA)

RMP	Risk management plan
SAE	Serious adverse event
SPECT	Single-photon emission computed tomography
SPECT/CT	Single-photon emission computed tomography / computed tomography
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
TRUS	Transrectal ultrasound

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for trofolastat in the above-mentioned medicinal product.

Diagnostic or therapeutic radiopharmaceutical
This application for a diagnostic radiopharmaceutical / therapeutic radiopharmaceutical has been reviewed by Swissmedic and the Expert Commission for Radiopharmaceuticals.

2.2 Indication and dosage

2.2.1 Requested indication

This medicinal product is for diagnostic use only.
After radiolabelling with sodium pertechnetate (^{99m}Tc) solution, technetium (^{99m}Tc) trofolastat is indicated for:

- SPECT of PSMA-positive lesions in men with high-risk prostate cancer and PSA levels ≥ 2 ng/ml
- Radio-guided surgery for intraoperative detection and removal of metastatic lesions in prostate cancer patients.

2.2.2 Approved indication

This medicinal product is intended for diagnostic use only.

After radiolabelling with sodium pertechnetate (^{99m}Tc) solution, technetium (^{99m}Tc) trofolastat solution for injection is indicated for:

- Selection of adult patients with metastatic prostate cancer for whom PSMA-targeted therapy is indicated.

2.2.3 Requested dosage

Summary of the requested standard dosage:
The standard dosage for adults is 740 ± 111 MBq.
There is no application for children and adolescents in the indication of prostate cancer.
No dose adjustment is necessary for elderly persons (> 65 years).
Use in patients with renal and hepatic disease has not been studied, careful consideration is required.
A table of radiation exposure for the organs is available.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	6 June.2023
Formal objection	28 June 2023
Response to formal objection	26 July 2023
Formal control completed	25 August 2023
List of Questions (LoQ)	19 March 2024
Response to LoQ	11 June 2024
2nd List of Questions (LoQ)	29 August 2024
Response to 2nd LoQ	20 December 2024
Preliminary decision	20 December 2024
Response to preliminary decision	17 February 2025
Labelling corrections and/or other aspects	23 April 2025
Response to labelling corrections and/or other aspects	25 May 2025
Final decision	8 August.2025
Decision	approval

3 Medical context

Prostate cancer is the second leading cause of cancer-related death among men in the US and the third leading cause of cancer-related death in Europe.[1,2]
Diagnostic workup of prostate cancer includes PSA testing, digital rectal palpation, transrectal ultrasound (TRUS), prostate biopsy, and histopathologic examination. For unfavourable intermediate, high risk, and very high-risk disease, NCCN guidelines (version 4.2024) recommend bone and soft tissue imaging. PSMA-PET/CT or PSMA-PET/MRI are considered alternatives to standard imaging of bone and soft tissue for initial staging, the detection of biochemically recurrent disease, and as workup for progression.
PSMA is a transmembrane protein with an extracellular binding site. PSMA tissue expression is high on the cell surface of prostatic tissue, including prostate cancer tissue.
[^{68}Ga]-PSMA-11 and [^{18}F]PSMA-1007 are available in Switzerland for the detection of PSMA-positive lesions in patients with prostate cancer.

SPECT/CT is a three-dimensional nuclear medicine imaging technique that combines information gained from scintigraphy with information from computed tomography. SPECT is widely used in most European countries and is considered cost-effective. However, there is currently no approved PSMA-targeting SPECT tracer in Europe.

According to expert consensus statements and guidelines, 99mTc-PSMA SPECT is considered an alternative modality for selecting patients for 177Lu-labelled PSMA-targeted radioligand therapy.[3,4]

[1] Siegel, RL, KD Miller, and A Jemal, 2020, Cancer statistics, 2020, CA Cancer J Clin, 70(1):7-30
[2] Malvezzi M et al., 2019, European cancer mortality predictions for the year 2019 with focus on breast cancer, Ann Oncol, 30(5):781-787
[3] Fanti S et al. EAU-EANM Consensus Statements on the Role of Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography in Patients with Prostate Cancer and with Respect to [177Lu]Lu-PSMA Radioligand Therapy. Eur Urol Oncol. 2022 Oct;5(5):530-536
[4] Kratochwil C et al. Joint EANM/SNMMI procedure guideline for the use of 177Lu-labelled PSMA-targeted radioligand-therapy (177Lu-PSMA-RLT). Eur J Nucl Med Mol Imaging. 2023 Jul;50(9):2830-2845

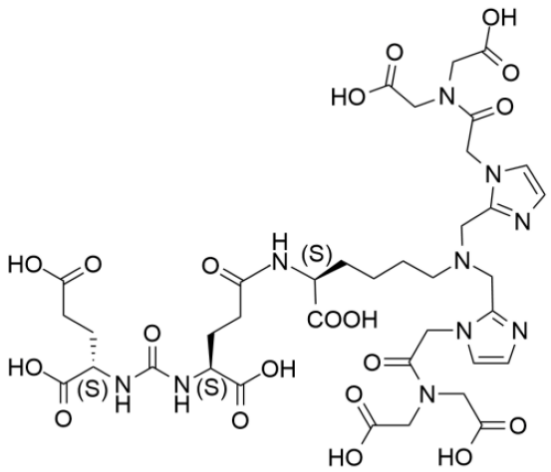
4 Quality aspects

The kit for the radiopharmaceutical preparation of technetium (^{99m}Tc) trofolastat includes a lyophilised powder (vial 1) intended for reconstitution with [^{99m}Tc]technetium chloride solution obtained from an approved radionuclide generator. The radionuclide is not part of the kit. After radiolabelling, the solution is neutralised with a 0.35 M HCl solution (vial 2).

4.1 Drug substance

Drug substance precursor (trofolastat)

INN:	n.a.
Former company Code:	MIP-1404
Chemical name:	(2S)-2-[[(1S)-4-[[(1S)-5-[bis[[1-[2-[bis(carboxymethyl)amino]-2-oxoethyl]imidazol-2-yl]methyl]amino]-1-carboxypentyl]amino]-1-carboxy-4-oxobutyl]carbamoylamino]pentanedioic acid
Molecular formula:	$C_{37}H_{50}N_{10}O_{20}$
Molecular mass:	954.9 g/mol
Molecular structure:	



Physicochemical properties:
White to off white, odourless, amorphous solid. Slightly to sparingly soluble in water; very soluble in aqueous acetonitrile; very soluble in methanol.

Synthesis:
Trofolastat is manufactured in a multi-step, convergent process. The chemical steps consist of amidation and other common organic synthesis steps through the use of protective groups. After final deprotection, the precursor is purified by preparative chromatography and lyophilised before packaging.

Specification:
In order to ensure a consistent quality of trofolastat, the specifications include all relevant test parameters as recommended by the relevant ICH guidelines. The analytical methods are adequately described and the non-compendial methods are fully validated in accordance with ICH guidelines.

Stability:
Appropriate stability data has been presented. Based on the results, a satisfactory re-test period has been established.

4.2 Drug product

Drug product – vial 1
Description and composition:
Vial 1 contains a lyophilised powder comprised of the active substance precursor trofolastat and several excipients, e.g. disodium boranocarbonate, tartaric acid, buffers, pH adjusters, and a bulking agent.

Pharmaceutical development:
The content of vial 1 was optimised in the course of pharmaceutical development. With the final vial formulation, the number of labelling steps has been reduced and technetium (^{99m}Tc) trofolastat yield has been improved. Manufacturing operations have to be conducted aseptically since the product cannot be terminally sterilised.

Manufacture:
The excipients and active substance precursor are dissolved and mixed in a specific order, accompanied by pH adjustment and sterile filtration. The components of the container closure system are sterilised prior to filling.

Specification:
Adequate tests and acceptance criteria for release and end of shelf life have been established for the control of the finished product (vial 1). The specifications include relevant physicochemical characteristics, identification of the drug substance precursor and several excipients, assays (precursor and some excipients) and purity tests, as well as sterility and bacterial endotoxin tests. The applied test methods are adequately validated according to the recommendations of the current scientific guidelines.

Container closure system:
The container closure system consists of a Type I glass vial which is closed with an elastic, coloured rubber stopper and capped with an aluminium flip-off cap.

Stability:
Appropriate stability data have been generated in the packaging material intended for commercial use and according to the relevant international guidelines. An appropriate shelf life has been proposed when stored at 2 °C – 8 °C.

Drug product – vial 2
Description and composition:
Vial 2 contains a neutralisation solution (0.75 mL 0.35 M HCl) consisting of hydrochloric acid and water for injection.

Pharmaceutical development:
The concentration of hydrochloric acid was optimised during development. The overfill of the solution is considered justified.

Manufacture:
The solution is prepared by mixing the excipients, followed by sterile filtration. The filled vials are then terminally sterilised.

Specification:
Adequate tests and acceptance criteria for release and end of shelf life have been established for the

control of the finished product (vial 2). The specifications include relevant physicochemical characteristics, identification of the excipient and its assay, as well as sterility and bacterial endotoxin tests. The applied test methods are compendial.

Container closure system:
The container closure system consists of a Type I glass vial which is closed with a rubber stopper and capped with an aluminium flip-off cap.

Stability:
Appropriate stability data have been generated in the packaging material intended for commercial use and according to the relevant international guidelines. An appropriate shelf life has been proposed when stored at 2 °C – 8 °C.

Radiolabelled drug product
Description and composition:
The kit radiopharmaceutical has a dosage strength of 80 µg trofolastat as a lyophilisate, which has to be reconstituted with a sodium[^{99m}Tc]-technetium-pertechnetate solution up to 4.44 GBq. The kit is intended for multidose use. RoTecPSMA is used for SPECT-CT, an alternative technique to PET-CT.

Pharmaceutical development:
The drug product RoTec-PSMA underwent several improvements during pharmaceutical development. The formulation is intended to stabilise the product, thus ensuring its effectiveness and stability over time. A first version of a two-vial preparation kit described in the pharmaceutical development was further developed and resulted in the final kit radiopharmaceutical, which consists of one vial containing all the components in lyophilised form necessary to perform the radiolabelling reaction. In addition to the vial containing the lyophilisate, the kit includes a second 10 ml vial containing 0.35 M HCl. This is used in the preparation of the ready-to-use solution.

Manufacture:
All development steps in the manufacturing process have been described. The necessary information on the batch formula is provided.

Specification:
Specifications with acceptance criteria for release and shelf life have been defined. Specifications for the RotecPSMA solution for injection include diverse tests and acceptance criteria, such as, for example, appearance of the lyophilised powder, appearance of the solution, diverse identity tests, physiologically relevant tests (including sterility, bacterial endotoxins, and pH), chemical purity tests, and radiochemical purity tests. These criteria ensure the quality and compliance of the RotecPSMA solution for injection.

Analytical methods:
Analytical test procedures are described only. The data and high-resolution chromatograms for the validation of analytical methods are acceptable and described in the corresponding chapters of Module 3.

Container closure system:
Vial 1 is a 10R colourless, Type I glass vial according to Ph. Eur. 3.2.1 with a lyophilisation stopper made of an elastic, coloured rubber material according to Ph. Eur. 3.2.9 and sealed with an aluminium cap with a plastic flip-off top. The container closure system of vial 2 consists of a 2R colourless, Type I glass vial according to Ph. Eur. 3.2.1 and is closed with a stopper made of a rubber material according to Ph. Eur. 3.2.9 and sealed with an aluminium cap with a plastic flip-off top.

Stability:
The stability of RotecPSMA was assessed under different environmental conditions during the radiopharmaceutical's validity period (an in-use stability study was performed for shelf life after radiolabelling). The drug products shelf life after radiolabelling is 12 hours when stored below 25°C after labelling.

4.3 Quality conclusions

Swissmedic:
Satisfactory and consistent quality of the drug substance precursor and the kit components has been demonstrated.

Expert Commission for Radiopharmaceuticals:
The product seems satisfactory and consistent in terms of the quality of its drug substance and drug product.
Product testing by an independent laboratory commissioned by Swissmedic resulted in a number of requests for improvement of the suggested radiochemical purity testing methods by HPLC and TLC. New batch data obtained from 3 batches following implementation of the changes have been submitted and are satisfactory.

5 Nonclinical aspects

5.1 Pharmacology

The rhenium surrogate of ^{99m}Tc-MIP-1404, MIP-1382, and MIP-1404 (unlabelled ligand) competitively inhibited binding of ^{123}I-MIP-1072 to LNCaP cells with IC_{50} values of 2 and 104 nM. In direct binding assays, ^{99m}Tc-MIP-1404 bound PSMA with a Kd of 1.71 nM. Thus, ^{99m}Tc-MIP-1404 is a specific, high-affinity ligand for prostate-specific membrane antigen (PSMA). Upon binding to PSMA on the cell surface, ^{99m}Tc-MIP-1404 was internalised into cells within minutes. ^{99m}Tc-MIP-1404 localised in PSMA-expressing tissues in vivo, i.e. the kidneys, which are also the primary organs of excretion, as well as PMSA-positive tumours.
Secondary pharmacology effects arising from binding to any target other than PSMA are unlikely. The results of the safety pharmacology studies raised no cardiovascular, central nervous system or respiratory safety concerns associated with the administration of MIP-1404.
The only potential safety concern associated with the administration of ^{99m}Tc-MIP-1404 is a potential pharmacodynamic drug interaction if it is combined with other potent PSMA ligands at the same time.

5.2 Pharmacokinetics

Protein binding of ^{99m}Tc-MIP-1404 in plasma was found to be moderate across all species tested. Following intravenous (IV) bolus administration, ^{99m}Tc-MIP-1404 was distributed in the total body fluids. Uptake and exposure were greatest in the kidneys, which express PSMA and have been identified as the primary organ of excretion. The drug was cleared rapidly and steadily from plasma in rats and dogs. The elimination half-life ($t_{1/2}$) in plasma was 5.09 hours in rats and 13.3 hours in dogs, which is similar to the $t_{1/2}$ in patients (6.02 h). The organ distribution study revealed that ^{99m}Tc-MIP-1404 was cleared rapidly from all other tissues. Up to 90% of the unmetabolised test article (both ^{99m}Tc-MIP-1404 and MIP-1382) was primarily found in the plasma and urine of both species. Pharmacokinetic drug interaction studies did not identify any risk.

5.3 Toxicology

The GLP-compliant single and repeat-dose toxicity and genotoxicity assessments were performed using MIP-1404 blended with MIP-1382 (rhenium labelled MIP-1404) at a ratio of 100:1. Two single-dose and two repat-dose studies were conducted in rats and dogs with intravenous administration up to 381.7/3.82 µg/kg in rats and 114.5/1.15 µg/kg in dogs. The MIP-1404/MIP-1382 formulation was well tolerated and no toxic effects were observed. MIP-1404 and MIP-1382 were not genotoxic and not mutagenic in vivo.

5.4 Nonclinical conclusions

The toxicological profile of ^{99m}Tc-MIP-1404 is considered to be sufficiently characterised. The submitted nonclinical data support its use as a radiodiagnostic imaging agent for localising PSMA-positive prostate cancer lesions. The relevant information has been included in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

A summary of the clinical pharmacology is provided in the Information for healthcare professionals in the appendix of this report.

6.2 Dose finding and dose recommendation

Not applicable.

6.3 Efficacy

The applicant two clinical studies evaluating the efficacy and safety of (^{99m}Tc) trofolastat in the primary staging of prostate cancer (PC) patients.
In addition, retrospective literature data were provided for the assessment of different clinical settings, including the selection of patients for PSMA-directed radioligand therapy.

Staging of prostate cancer with (^{99m}Tc) trofolastat

Phase 2 study MIP-1404-201 evaluated the diagnostic performance of (^{99m}Tc) trofolastat SPECT/CT compared to MRI in newly diagnosed prostate cancer patients at high risk for metastatic disease. Even though the sensitivity achieved by (^{99m}Tc) trofolastat for patients' prostate glands was higher than by MRI ((^{99m}Tc) trofolastat vs MRI sensitivities 93.8% vs 85.4% for subjects' prostate glands and 40.4% vs 44.4% for evaluable prostate segments), this study did not include a direct comparison with PSMA-PET/CT. Sensitivity in detecting pelvic lymph node involvement was moderate, as it is also for MRI (25.0% vs 12.5%). No hypothesis was tested within this study, and the statistics were descriptive only.

Phase 3 study MIP-1404-3301 was a multi-reader, open label, phase 3 study assessing the safety and efficacy of (^{99m}Tc) trofolastat imaging to detect clinically significant PC in men with biopsy-proven low-grade PC who were candidates for active surveillance. The diagnostic performance evaluated by three independent, blinded, central readers was compared to central histopathological evaluation in patients following radical prostatectomy or after prostate biopsy. The specificity of (^{99m}Tc) trofolastat imaging in detecting clinically significant prostate cancer ranged from 71% to 75% and was statistically significant. However, the other co-primary endpoint for the sensitivity of (^{99m}Tc) trofolastat imaging in determining clinically significant prostate cancer was not met and ranged from 47% to 51%.

Taken together, the data provided were not considered sufficient to allow the use of (^{99m}Tc) trofolastat SPECT/CT in primary staging.

Radioguided surgery
Only limited preliminary data were available for this approach and the unclear impact on oncological outcome did not justify the indication.

Selection of prostate cancer for PSMA-based therapy using (^{99m}Tc) trofolastat
This indication was requested by the applicant in response to the list of questions during the review procedure.

Although the (^{99m}Tc) trofolastat SPECT/CT system has a lower resolution and consequently a lesser ability to detect small-sized lesions compared to PET/CT, the identification of PSMA-positive lesions in patients with known metastatic disease is considered a reasonable indication. This clinical situation does not require a high-granularity imaging modality as the presence of PSMA-positive lesions is sufficient for treatment selection in this later-line disease setting. According to international consensus recommendations (European Association of Nuclear Medicine and Society of Nuclear Medicine and Molecular Imaging), (^{99m}Tc) trofolastat SPECT/CT is an alternative to ^{68}Ga]-PSMA- or [18F]-PSMA-PET in this indication. Retrospective data were provided to support this indication. When compared, (^{99m}Tc) trofolastat SPECT/CT and 68Ga-PSMA-11 PET/CT displayed a similar maximum standardised uptake value (SUVmax) (see Information for Healthcare Professionals for further information).

6.4 Safety

Overall, (^{99m}Tc) trofolastat was well tolerated and no serious adverse events or deaths were reported. In phase 3 study MIP-1404-3301, 14.2% of all patients experienced a treatment-emergent adverse event (TEAE) of any grade, most of which were grade 1-2 (13.6%). The most frequently reported TEAEs (incidence ≥1%) were headache, dizziness, fatigue, and nausea. Please refer to the Information for Healthcare Professionals for information on the pooled safety data from 629 study participants exposed to (^{99m}Tc) trofolastat.

6.5 Final clinical benefit risk assessment

The final benefit-risk assessment was positive for the use of (^{99m}Tc) trofolastat SPECT/CT in the identification of PSMA-positive lesions in metastatic prostate cancer patients intended for PSMA-targeted therapy.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for RotecPSMA was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

RoTecPSMA 80 µg multi-dose kit for radiopharmaceutical preparation

Composition

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

Vial 1: RoTecPSMA - Lyophilisate
Active substance: 80 µg trofolastat
Excipients:
Disodium borate carbonate
2.85 mg Disodium tetraborate decahydrate
Tartaric acid
Sodium carbonate anhydrous
Sodium hydroxide

Vial 2: RoTecPSMA - Solution
0.75 ml solution with 0.35 M HCl
Excipients:
Hydrochloric acid
Water for injection

Sodium content
Vial 1 contains 5.17 mg of sodium.
Vial 2 does not contain sodium.

Pharmaceutical form and quantity of active substance per unit
RoTecPSMA is a multidose kit for the radiopharmaceutical preparation of technetium (^{99m}Tc) trofolastat.
Vial 1: white to almost white lyophilised powder
Vial 2: clear, colourless solution
For radiolabelling with sodium (^{99m}Tc) pertechnetate solution.

Indications/Potential uses
This medicinal product is intended for diagnostic use only.

After radiolabelling with sodium pertechnetate (^{99m}Tc) solution, technetium (^{99m}Tc) trofolastat solution for injection is indicated for:

- Selection of adult patients with metastatic prostate cancer for whom PSMA-targeted therapy is indicated.

Dosage/Administration

The medicinal product is intended exclusively for use in institutions authorised to use radionuclides.

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.

Adults

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

Elderly patients

No special dosage regimen for elderly patients is required.

Children and adolescents

Technetium (^{99m}Tc) trofolastat is not approved for use in the paediatric population.

Patients with renal impairment/hepatic impairment

The safety and efficacy of technetium (^{99m}Tc) trofolastat have not been studied in patients with hepatic 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 “Warnings and precautions”).

Precautions to be taken before handling or administering the medicinal product

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

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

Image acquisition

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

The patient should be positioned supine with the arms above the head, as tolerated by the patient. 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. Patients should void immediately prior to image acquisition. 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.
A CT scan should be obtained for attenuation correction and anatomical correlation.

Radiation exposure/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 x 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 (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.

Contraindications

Hypersensitivity to the active substance, to any of the listed excipients, or to any of the components of the radiolabelled radiopharmaceutical.

Warnings and precautions

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 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.

Radiation risk

Technetium (^{99m}Tc) trofolastat contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. Ensure safe handling and reconstitution procedures to minimise the risk of radiation exposure to patients and healthcare workers (see section «Dosage/Administration» and section «Other information, Instructions for use and handling»).

Renal impairment / Hepatic impairment

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

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

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. Patients should be well hydrated prior to technetium (^{99m}Tc) trofolastat administration and advised to urinate immediately prior to image acquisition.

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

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

Limitations of use

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

After the procedure

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

Close contact with infants and pregnant women should be avoided during the first 24 hours after administration of the radiopharmaceutical.

Other information

Specific warnings

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

Interactions

No interaction studies have been performed.

In vitro evaluation of drug interaction potential

CYP450 enzymes

In vitro, trofolastat is not a substrate of cytochrom P450 (CYP450) enzymes, not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 and not an inductor of CYP1A2, CYP2B6, CYP2C9 and CYP3A. Technetium (^{99m}Tc) trofolastat is not expected to have any drug interactions with CYP450 substrates, inhibitors or inductors.

Transporters

Trofolastat is neither a substrate of P-gp nor an inhibitor of P-gp. Therefore, no drug interactions with the P-pg transporter are to be expected with technetium (^{99m}Tc) trofolastat.

Interactions between new-generation anti-hormonal therapy and PSMA PET have been described in the literature and should be taken into account when interpreting PSMA SPECT images.

Pregnancy/Breast-feeding

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

Fertility

No studies on fertility have been performed.

Effects on ability to drive and use machines

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

Adverse effects

Summary of the safety profile

The overall safety profile of technetium (^{99m}Tc) trofolastat is based on data from its use in 629 study participants.

Mild to moderate adverse events occurred after administration of technetium (^{99m}Tc) trofolastat, with the exception of 3 individual grade 3 events (0.5 %: hypertension, presyncope, neck pain). No serious adverse events occurred.

The most common adverse drug reactions of any grade (incidence ≥ 0.5 %) are headache (1.7 %), dizziness (0.8 %) and fatigue (0.6 %).

Tabulated summary of adverse drug reactions by MedDRA system organ class.

The frequencies listed 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); unknown (cannot be estimated form the available data).

Although the adverse reactions may occur less frequently in reality than stated here , classification in a frequency group lower than 'uncommon' (≥ 1/1,000, < 1/100) is not possible due to the size of the database.

System Organ Class	**Adverse reaction**	**Frequency**
Nervous system disorders	Headache	Common
	Dizziness, dysgeusia, paraesthesia, presyncope, somnolence, tension headache	Uncommon
General disorders and administration site conditions	Fatigue, injection site extravasation, influenza like illness, oedema peripheral	Uncommon
Vascular disorders	Hypertension, flushing, hot flush, orthostatic hypotension	Uncommon
Gastrointestinal disorders	Nausea, abdominal discomfort, toothache	Uncommon
Investigations	Aspartate aminotransferase increased, blood bilirubin increased, blood pressure increased	Uncommon
Eye disorders	Eye irritation, vitreous floaters	Uncommon
Immune system disorders	Drug hypersensitivity	Uncommon
Musculoskeletal and connective tissue disorders	Myalgia, neck pain	Uncommon
Renal and urinary disorders	Chromaturia	Uncommon

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 suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reactions via the online portal ElViS (Electronic Vigilance System).
You can find further information at www.swissmedic.ch.

Overdose

In the event of an overdose with technetium (^{99m}Tc) trofolastat the absorbed dose should be reduced as far as possible. This can be achieved by drinking fluids and increasing the elimination of the radionuclide through frequent bladder and bowel emptying. It might be helpful to estimate the effective dose that was applied.

Properties/Actions

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 PSMA-positive prostate cancer cells.

Pharmacodynamics

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

Clinical efficacy

The safety and efficacy of technetium (^{99m}Tc) trofolastat was evaluated in a total of seven clinical studies.

With regard to the application for selecting patients with metastatic prostate cancer for radioligand therapy with ^{177}Lu-PSMA, Cook et al. 2023 (J Nucl Med 2023; 64:227–231) investigated the use of technetium (^{99m}Tc) trofolastat. To this end, two cohorts of patients with metastatic castration-resistant prostate cancer were analysed, which matched in terms of age, prostate-specific antigen (PSA) and Gleason total score and in which either technetium (^{99m}Tc) trofolastat SPECT/CT or ^{68}Ga-PSMA-11 PET/CT had been performed. Each cohort consisted of 25 patients. Comparison of the data showed that the median SUV_{max} value of technetium (^{99m}Tc) trofolastat SPECT/CT lesions did not differ significantly from that of ^{68}Ga-PSMA-11 PET lesions (median 18.2 vs. 17.3). However, the technetium (^{99m}Tc) trofolastat liver SUV_{max} was higher (median 8.5 vs. 5.8) and the lesion–to–liver ratio was lower (median 2.7 vs. 3.5). For use in patient selection, it is crucial that there was no significant difference between the two groups in terms of SUV_{max} of the parotid gland or the ratio between lesion and parotid gland.

Pharmacokinetics

Absorption

Not applicable.

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 2 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.

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.

Metabolism

Following a single intravenous injection in healthy subjects and patients with prostate cancer, unchanged technetium (^{99m}Tc) trofolastat was the predominant component in urine. Further comprehensive studies on the metabolism of technetium (^{99m}Tc) trofolastat have not been conducted in humans.

Elimination

The activity is excreted via the renal route, but excretion via faeces has not been investigated 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 % to 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.

Kinetics of specific patient groups

Not applicable.

Preclinical data

Pre-clinical data based on conventional studies of safety pharmacology and toxicity following repeated administration did not reveal any specific hazards for humans.

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

Other information

Incompatibilities

This medicinal product may only be mixed with the medicinal products specified under “Instructions for use and handling”.

Shelf life

RoTecPSMA must not be used after the expiry date (= EXP) stated on the packaging.

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

Special precautions for storage

Store in the refrigerator (2 - 8 °C).

Storage of the radiolabelled product must meet the legal requirements on the storage of radioactive materials.

Instructions for handling

Special precautions for disposal and other handling

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.

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. Effective shielding of the radiation is mandatory.

The content of the kit before extemporary preparation is not radioactive. After sodium pertechnetate (^{99m}Tc) (Ph. Eur.) is added, effective shielding of the final preparation must be maintained.

The administration of radiopharmaceuticals poses risks to other persons due to external radiation or contamination from spilled urine, vomiting or other biological fluids. Therefore, radiation protection precautions must be taken in accordance with national regulations.

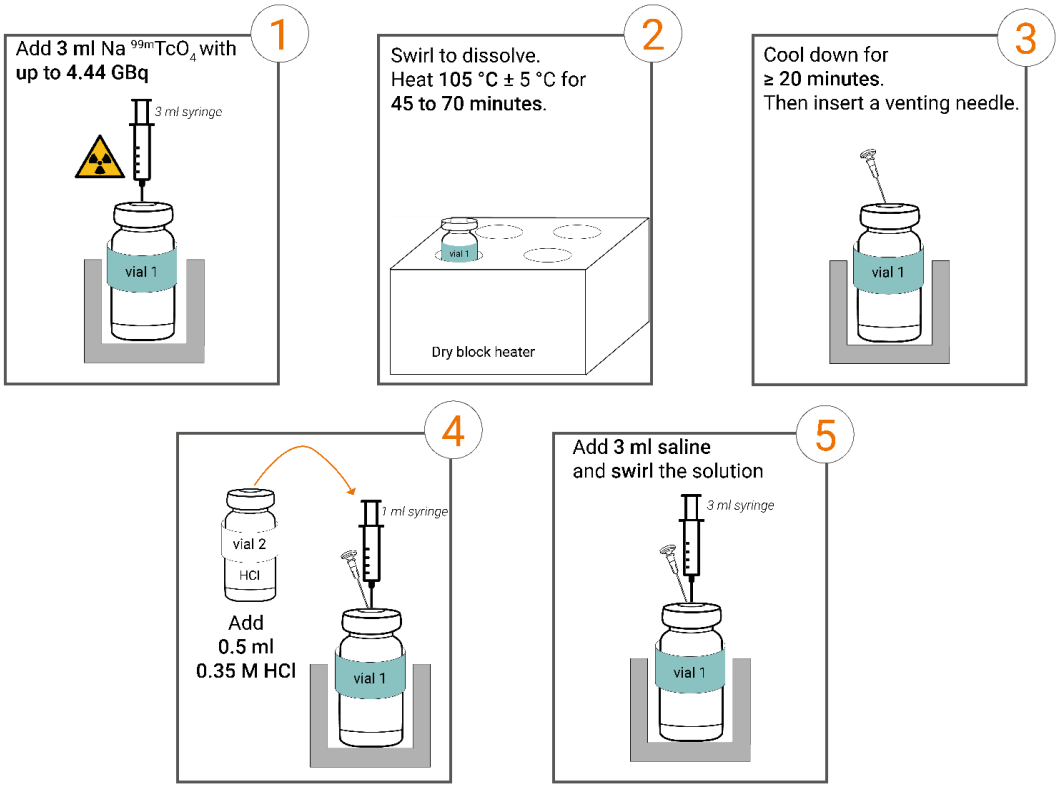
Any unused medicinal product or waste material should be disposed of in accordance with applicable Swiss radiation protection regulations.

<u>Preparation</u>

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

The vials must not be used 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.



(1) Set the heating block so that a temperature range of 105 ± 5 °C is reached at the vial (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 in a lead shield equipped with a shielded lid.

(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 0.9 % saline to dilute the sodium pertechnetate (^{99m}Tc) solution to the desired concentration prior to addition to vial 1.

Note: Make sure that the heating block has reached 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 heating block and allow vial 1 to heat for 45 to 70 minutes.

(8) Remove vial 1 from the heating block and place it in the 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. Next, inject 3 ml of isotonic

saline solution into vial 2. 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 shielded 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 12 hours from the time of preparation.

Properties of the product after radiolabelling:

Appearance: clear, colourless and without undissolved matter
pH: 5 - 8

Quality Control

To calculate radiochemical purity using thin-layer chromatography (TLC), the two procedures below (procedure 1 and procedure 2) must be carried out in accordance with the following instructions.

Chromatographic system:

TLC plate:	2x ITLC-SA strips (2 cm wide strips recommended)
Solvent:	Use of 2x chromatographic chambers with cover
	Water for injection (WfI) for procedure 1
	Methyl ethyl ketone (MEK) for procedure 2
Sample volume:	10 - 15 µl
Start:	1.5 cm from the bottom edge of the plate
Running distance:	5 cm
Detector:	Suitable detector

Method:

(1) Fill the chromatography chambers with the appropriate solvents (WfI or MEK, depending on the procedure) to a maximum height of 0.5 cm. Then cover the chambers to allow the solvent vapour to equilibrate.
(2) Marking the ITLC-SA strips with a pencil is recommended as follows:

- at 1.5 cm from the bottom edge of the plate (starting line)
- at 4 cm from the bottom edge of the plate (integration border/ cutting position; R_f = 0.5)
- at 6.5 cm from the bottom edge of the plate (end of running distance)

(3) Apply one drop (10 - 15 µl) of the sample solution in the center of the starting line. It is recommended to allow the spot to dry for at least 10 minutes.

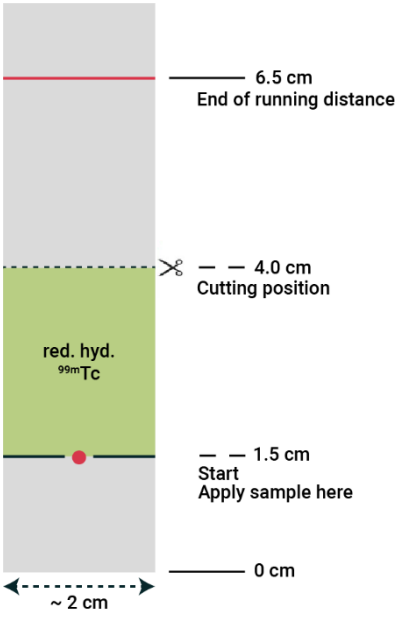
Note: Please note the detection limit of the detector and the minimum activity required for the sample drop.

(4) Place one ITLC-SA strip upright in each chamber and ensure that the spots of the sample are above the solvent surface. Make sure that the strip does not touch the walls of the chamber at any point. 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 (maximum 2 hours).

TLC procedure 1: Determination of reduced, hydrolysed (^{99m}Tc) technetium (red. hyd. ^{99m}Tc, impurity A)

Solvent: WfI

Chemical compound	Sections
red. hyd. ^{99m}Tc (**Impurity A**)	below the cutting position (R_f: < 0.5)
[^{99m}Tc]pertechnetat + [^{99m}Tc]trofolastat	above the cutting position (R_f: > 0.5)



Evaluation:

The red. hyd. ^{99m}Tc (impurity A) remains at the starting point.
If you don't have access to a TLC scanner, cut strip 4 cm from the bottom edge of the plate. Measure the radioactivity of both sections separately. Put the activity of the lower section in relation to the total activity..

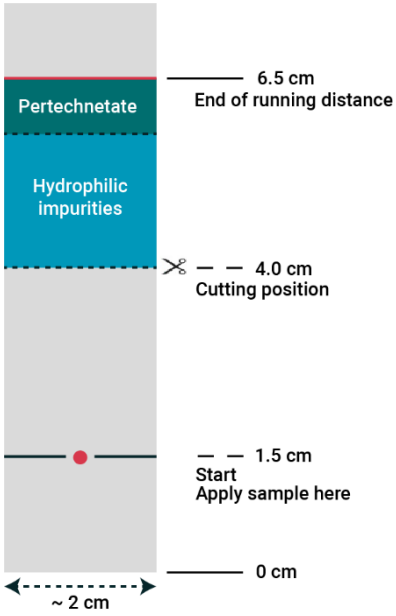
Calculation:

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

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

Solvent: MEK

Chemical compound	Sections
red. hyd. ^{99m}Tc + [^{99m}Tc]trofolastat	below the cutting position (R_f: < 0.5)
[^{99m}Tc]pertechnetat (**impurity B**) + hydrophilic impurities (**impurity C**)	above the cutting position (R_f: > 0.5)



Evaluation:

[^{99m}Tc]pertechnetate (impurity B) and hydrophilic impurities (impurity C) move with the solvent front.

If you don't have access to a TLC scanner, cut strip 4 cm from the bottom edge of the plate. Measure the radioactivity of both sections separately. Put the activity of the upper section in relation to the total activity.

Calculation:

$$\text{Impurity B [\%]} + \text{C [\%]} = \frac{\text{Activity of the uppersection}}{\text{Total Activity of the strip}} \text{ x } 100\ \%$$

Calculation of radiochemical purity (RCP, Specification ≥ 90%):

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

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

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

Radiation protection warning

The use of radioactive substances on humans is regulated by law through the Radiological Protection Ordinance (SR 814.501) and the Regulation on the Handling of Open Radioactive Sources (SR 814.554). A permit from the Federal Office of Public Health is required for handling radioactive substances. When handling radioactive substances and disposing of all radioactive waste, the protective precautions of the above-mentioned ordinance must be observed in order to avoid any unnecessary exposure to radiation for patients and staff. Radiopharmaceuticals should be prepared by the user in accordance with the requirements for radiation safety and pharmaceutical quality. Appropriate aseptic precautions should be taken.

Marketing authorisation number

69451

Packages

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

Pack sizes:

2 Kits (vial 1 und vial 2)

5 Kits (vial 1 und vial 2)

Sales category [A]

Marketing authorisation holder

medeo AG, 5405 Baden

Information last revised

December 2024