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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

SWAN-PSMA-1007

International non-proprietary name:	[^{18}F]PSMA-1007
Pharmaceutical form:	solution for injection
Dosage strength(s):	222 MBq / ml
Route(s) of administration:	intravenous
Marketing authorisation holder:	SWAN Isotopen AG
Marketing authorisation no.:	67370
Decision and decision date:	approved on 11 June 2024

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.

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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
ASCO	American Society of Clinical Oncology
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
BCP	Biochemical persistence
BCR	Biochemical recurrence
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CT	Computed tomography
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
DMSO	Dimethyl sulfoxide
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOS	End of synthesis
ERA	Environmental risk assessment
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration (USA)
FCH	[^{18}F]fluorocholine
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
MRI	Magnetic resonance imaging
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

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
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)

New active substance status
The applicant requested new active substance status for [^{18}F]PSMA-1007 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

SWAN-PSMA-1007 is a radiodiagnostic preparation for imaging pathological changes by positron emission tomography (PET), which are associated with increased expression of prostate-specific membrane antigen (PSMA). SWAN-PSMA-1007 can be used, for example, to visualise tumour foci in patients with adenocarcinoma of the prostate (prostate carcinoma).
SWAN-PSMA-1007 cannot be used for therapeutic purposes.

2.2.2 Approved indication

SWAN-PSMA-1007 ([^{18}F]PSMA-1007) is a radiodiagnostic agent indicated for the imaging detection of prostate-specific membrane antigen (PSMA)-positive lesions with positron emission tomography (PET) in adult patients with prostate cancer.

2.2.3 Requested dosage

Summary of the requested standard dosage:

The standard dosage for adults is 3 - 4 MBq/kg body weight, with a maximum dose not to be exceeded of 360 MBq.
The medicinal product has not been tested in children or adolescents. In case of hepatic impairment, the dose should be moderately reduced.
No dose adjustment is necessary for elderly persons (> 65 years) or for persons with renal dysfunction.
A table of radiation exposures for the organs is available.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	23 November 2022
Formal objection	12 December 2022
Response to formal objection	2 February 2023
Formal control completed	16 February 2023
List of Questions (LoQ)	13 July 2023
Response to LoQ	9 November 2023
Preliminary decision	12 January 2024

Response to preliminary decision	28 March 2024
Final decision	11 June 2024
Decision	approval

3 Medical context

Diagnostic work-up of prostate cancer includes PSA testing, digital rectal palpation, transrectal ultrasound (TRUS), prostate biopsy, and histopathological examination. Additionally, further imaging techniques such as magnetic resonance imaging (MRI), bone scintigraphy, computed tomography (CT), and positron emission tomography (PET)/CT with different PET tracers are used.
Before March 2023, [^{18}F]fluorocholine was the only radioactive PET diagnostic agent authorised for the indication of prostate cancer in Switzerland.

Given the limitations of the most widely investigated PET tracers, targeting PSMA with molecular imaging agents has been increasingly investigated. PSMA is a transmembrane protein with an extracellular binding site. PSMA tissue expression is high on the cell surface of prostatic tissues affected by prostate cancer. However, despite the name, PSMA is not specific to prostate tissue. The PSMA protein can be found in low concentrations in many other organs[1]. Most adenocarcinomas of the prostate gland express high levels of PSMA in primary and metastatic lesions[2].
Since March 2023, [^{68}Ga]PSMA-11 has been authorised as a PSMA-specific PET tracer for the detection of PSMA-positive lesions in patients with prostate cancer in Switzerland.
Currently, several guidelines highlight the superior accuracy of PSMA-ligand PET/CT for the staging of primary disease in prostate cancer (European Association of Urology [EAU], European Society for Medical Oncology [ESMO], National Comprehensive Cancer Network [NCCN]), or consider additional value in this setting (American Society of Clinical Oncology [ASCO]). PSMA-ligand PET/CT evaluation of biochemical recurrence (BCR) or biochemical persistence (BCP) of prostate cancer is recommended in documents produced by the EAU, ASCO, and NCCN.

[1] Fendler WP et al., PSMA PET/CT: joint EANM procedure guideline/SNMMI procedure standard for prostate cancer imaging 2.0, Eur J Nucl Med Mol Imaging. 2023 Apr;50(5):1466-1486
[2] Mannweiler S et al., Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. Pathol Oncol Res. 2009;15:167–72; Bostwick DG et al. Prostate-specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer. 1998;82:2256–61

4 Quality aspects

4.1 Drug substance

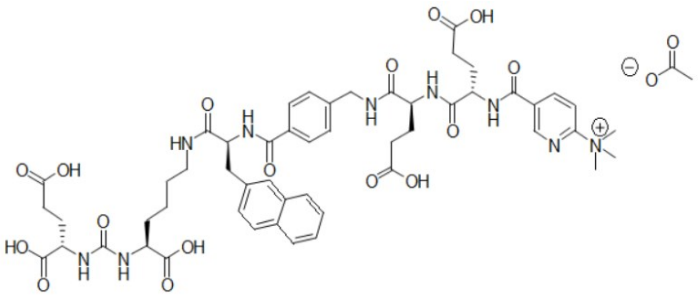
Precursor (non-radioactive): PSMA-1007

Chemical name: 5-((S)-4-carboxy-1-((S)-4-carboxy-1-(4-((S)-1-((S)-5-carboxy-5-(3-((S)-1,3-dicarboxypropyl)ureido)pentylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-ylcarbamoyl)benzylamino)-1-oxobutan-2-ylamino)-1-oxobutan-2-ylcarbamoyl)-*N*,*N*,*N*-trimethylpyridin-2-aminium acetate

Molecular formula: $C_{52}H_{64}N_9O_{16}$ x CH_3COOH

Molecular mass: 1071.12 g/mol

Molecular structure:



Physicochemical properties:
White to off-white solid, slightly soluble in water and soluble in dimethyl sulfoxide.

Synthesis:
PSMA-1007 precursor is obtained by adopting solid-phase synthesis starting from 2-CTC resin. After coupling the amino acid derivatives and, finally, the building block with the quaternary amine moiety to the resin, the crude product is cleaved from the solid support and deprotected, followed purification by preparative HPLC. Salt exchange is then performed by preparative HPLC using a mobile phase containing acetic acid, and PSMA-1007 precursor is finally isolated by concentration and lyophilisation. Pre-defined amounts of the solid bulk material are transferred into the final vials and flushed with argon before stoppers and caps are placed on the vials and crimped.

Specification:
In order to ensure a consistent quality of PSMA-1007 precursor, 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 the ICH guidelines.

Stability:
Appropriate stability data have been presented. Based on the results, a satisfactory shelf-life has been established when stored at −20 °C ± 5°C in the hydrolytic type I glass vials, closed by a chlorobutyl rubber stopper with a FluroTec™ barrier film and capped with a tear-off crimp.

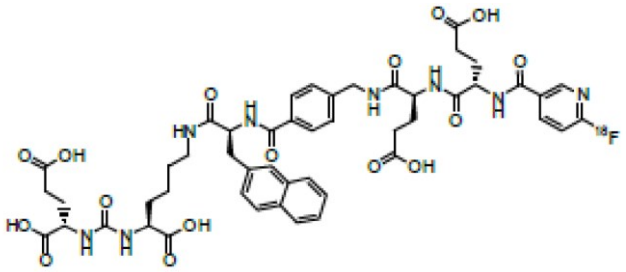
Drug Substance (radioactive): [^{18}F]PSMA-1007

Chemical name: (3S,10S,14S)-1-(4-(((S)-4-carboxy-2((S)-4-carboxy-2-(6[^{18}F]fluoronicotinamido)butanamido)butanamido)methyl)-phenyl)-3-(naphthalen-2-ylmethyl) 1,4,12-trioxo-2,5,11,13-tetraazahexadecane-10,14,16-tricarboxylic acid

Molecular formula: $C_{49}H_{55}{}^{18}FN_8O_{16}$

Molecular mass: 1030.01 g/mol

Molecular structure:



Physicochemical properties:
[^{18}F]PSMA-1007 is a radioactive drug substance with a half-life of 110 minutes (rounded). The decay mode is β^+ (96.7%) and electron capture (3.3%).

Synthesis:
The Drug Substance is manufactured in a radiosynthesis from non-radioactive precursor material, PSMA-1007 precursor, and the 18F-fluoride-radionuclide (generated by means of an accelerated cyclotron proton beam via the nuclear reaction: $^{18}O(p,n)^{18}F$). The radiosynthesis of [^{18}F]PSMA-1007 is a nucleophilic aromatic substitution reaction performed by heating the precursor in DMSO in the presence of a base. The reaction is carried out in an automated radiosynthesis module and takes place in a disposable cassette with reagent kits. The radiolabelling reaction is stopped by diluting the reaction mixture with an ethanol solution and then by loading it on a silica C18-cation cartridge. The resulting trapped Drug Substance is rinsed with a washing solution and then eluted with an ethanolic solution, diluted with a PBS-sodium ascorbate solution and sterilised via a 0.22 μm sterile filter. Next, the product is formulated by adding phosphate-buffered saline through the sterile filter.

Specification and Stability: see next paragraph.

4.2 Drug product

Description and composition:
SWAN PSMA-1007 is a radiopharmaceutical used for PET diagnostic imaging. It contains fluorine-18 and is administered intravenously. It is provided as a sterile, clear and colourless solution in a multi-dose vial. The radioactive concentration is 222 MBq per millilitre (±10%) at calibration time and date. The dispensed volume per vial ranges from 1 ml to 10 ml, corresponding to a radioactivity ranging from 222 MBq to 2220 MBq at calibration time. The drug product's shelf life is defined as 10 hours after the end of synthesis (EOS). It includes various components such as [^{18}F]PSMA-1007 as active substance, and the excipients disodium hydrogen phosphate, potassium dihydrogen phosphate, sodium chloride, potassium chloride, water for Injections, ethanol, and sodium ascorbate. The maximum injectable volume is 10 ml.

Pharmaceutical development:
The drug product SWAN [^{18}F]PSMA-1007 underwent improvements in its composition. The formulation aims to achieve product stabilisation and minimise radiolysis, ensuring the drug's effectiveness and stability over time. Several experiments for stabilisation of the product with sodium ascorbate were carried out. When higher amounts of sodium ascorbate (100-400 mg) were used, the decomposition of the drug product at high radioactivity concentrations (3.2-4.5 GBq/ml) was reduced. Adding 400 mg of sodium ascorbate was found to be the appropriate quantity to stabilise the drug product. All necessary information is provided and complete.

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

Specification:
The specifications for the SWAN [^{18}F]PSMA-1007 solution for injection include appearance of the solution, radioactivity concentration, identity tests (such as gamma emission energy, half-life, and retention time of [^{18}F]PSMA-1007 and [^{19}F]PSMA-1007), microbiological tests (including sterility, bacterial endotoxins), purity tests (radiochemical purity, chemical purity, tetrabutylammonium carbonate, ethanol, dimethyl sulfoxide, sodium ascorbate) and pH value. These criteria ensure the quality and compliance of the SWAN-PSMA-1007 solution for injection. Analytical test procedures are described in detail and have been validated.

Container Closure System:
SWAN PSMA-1007 is supplied in 15 ml sterile, colourless penicillin-type glass vials of Ph. Eur. Type I quality. These vials are closed with a rubber septum and an aluminium seal. Vials contain variable doses of [^{18}F]PSMA-1007 and are intended for multi-dose use, with 222 MBq/ml at calibration time, and a maximum volume of 10 ml.

Stability:
The stability of SWAN [^{18}F]PSMA-1007 was assessed up to 40°C throughout the radiopharmaceutical's validity period (10 hours). Measurements were taken at T0, T4, T8 and T10. Validation data were provided for a suitable number of batches and met all specifications. All specifications have been met at the investigated time points. The finished drug product is stable over the shelf life of 10 hours after EOS. Trends of radiochemical purity have been investigated.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

[^{19}F]PSMA-1007 bound with high affinity to the prostate-specific membrane antigen in a competitive binding assay in the nanomolar range of 4.2 and 6.7 nM in two independent experiments. [^{18}F]PSMA-1007 had a high internalisation rate of 68.9% *in vitro*. This high rate of internalisation, in addition to the high binding affinity, supports its use as a radioimaging ligand. [^{18}F]PSMA-1007 was taken up rapidly by tumour cells in nu/nu mice bearing lymph node carcinoma of the prostate (LNCaP) tumours, reaching a maximum within a few minutes and remained stable over time (140 min). The absolute uptake of [^{18}F]PSMA-1007 in PSMA-positive tumours was significantly higher than that of comparable radioimaging agents.
No secondary off-target activity of [^{18}F]PSMA-1007 is expected. Due to the low radiation intensity, a direct cytotoxic effect induced by the radiation of [^{18}F]PSMA-1007 is unlikely, as both the type of radiation (positron emission) and the radiation dose are optimised for imaging purposes.
No dedicated safety pharmacology studies have been conducted. In a GLP-compliant extended single-dose toxicity study, rats did not show any adverse clinical signs when treated with intravenous injections of up to 1430 µg/kg [^{19}F]PSMA-1007. This corresponded to 1000-fold exposure of the highest intended human mass dose (100 µg single dose, in a patient with body weight of 70 kg). [^{18}F]PSMA-1007 at 10^{-8} to 10^{-4} M had no effect on the hERG channel.

5.2 Pharmacokinetics

After intravenous administration, [^{18}F]PSMA-1007 exposure declined rapidly within 10 minutes in mice. Concomitantly, tissue concentrations were highest at 10 minutes post-injection. Plasma concentration reached about 5% of the injected dose after 60 minutes.
[^{18}F]PSMA-1007 was highly bound to serum albumin. It distributed to the whole body, where it rapidly accumulated in cells with high PSMA expression, i.e. tumour cells and kidneys. [^{18}F]PSMA-1007 was highly stable in human plasma with no degradation observed over a period of 4 h at 37°C. *In vivo*, only very low levels of metabolites were observed, amounting to 2% of the total activity in the urine and 4% in the kidneys at 1 h post injection. Urine was the major route of elimination in mice, whilst the hepatobiliary clearance was the main elimination route in humans.

5.3 Toxicology

Toxicity and the toxicokinetic profile of PSMA-1007 was investigated in a GLP extended single-dose toxicity study in rats with intravenous administration up to 1430 µg/kg body weight. PSMA-1007 treatment was well tolerated and no toxicological effects were observed. No repeat-dose toxicity studies have been conducted in accordance with the ICH M3 guideline on microdose trials. PSMA-1007 was not genotoxic *in vitro*. No carcinogenicity or reproductive toxicity studies were conducted.

5.4 Nonclinical conclusions

The toxicological profile of [^{18}F]PSMA-1007 is considered to be sufficiently characterised. The submitted nonclinical data support its use as a radiodiagnostic agent. The relevant information has been included in the Information for healthcare professionals, although some revision is needed.

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

No particular dose-finding studies were conducted by the Applicant or were reported in the literature either.
The currently available published studies demonstrated that a sufficient signal intensity could be reached with the application of a total radioactivity dose between approximately 100 MBq and 450 MBq.
The proposed dose of [^{18}F]PSMA-1007 solution for injection is 3-4 MBq/kg bodyweight (210-280 MBq for a 70 kg patient), with a maximum dose of 450 MBq. This is within the reported radioactivity doses reported in the literature on comparable human studies.

6.3 Efficacy

The main efficacy data were derived from the controlled, randomised, phase 3, pivotal study ABX-CT-301.
This study investigated [^{18}F]PSMA-1007 vs [^{18}F]fluorocholine (FCH) PET in patients with biochemical recurrence (BCR) after previous definitive treatment of localised prostate cancer. The comparator arm was considered acceptable given that FCH was the only PET tracer specifically authorised for prostate cancer in Switzerland at that time.
The study was initiated in March 2019 and completed in October 2020 at six study sites in France. A total of 200 patients were enrolled, and 195 of them received at least one study drug.
The primary objective of the study was to show superiority of [^{18}F]PSMA-1007 vs FCH PET based on the patient-based detection rate of all lesions compared with an expert panel assessment (standard of truth) as determined in an independent image read by three readers blinded to clinical data and tracer. The expert panel, consisting of a urologist, a radiologist, and a nuclear physician, had access to all imaging assessments from the clinical side (except the study PET examinations) together with clinical information (medical history, concomitant medications, procedures, results).
The detection rate was tested using a z-test based on generalised estimation equations (GEEs) at a one-sided level of significance of 2.5% each. Secondary endpoints included sensitivity, specificity, accuracy, positive and negative predictive value of [^{18}F]PSMA-1007 and FCH, which were analysed only descriptively. No target value was defined prospectively for specificity and sensitivity, and no superiority hypothesis was defined for the respective differences.

Patients with BCR after initial radical treatment were randomised to either [^{18}F]PSMA-1007 PET followed by FCH PET or to FCH PET followed by [^{18}F]PSMA-1007. The second PET examination was performed between 24 hours and 240 hours (10 days) after the first PET. Safety follow-up was 24h after the second PET CT. Patients were to be followed for 6 months for diagnostic and therapeutic procedures.
[^{18}F]PSMA-1007 was administered as a single intravenous injection of 3-4 MBq/kg (corresponding to an activity of 210-280 MBq for a 70 kg adult). FCH was similarly administered with an activity of 200-400 MBq.

Of the 195 patients with at least one dose of study drug, 190 underwent PET imaging with both study drugs.
Median age was 69 years. Most of the patients had a Gleason score of 7 (124/195). The median PSA level was slightly lower in the “FCH first” group (1.27 ng/ml vs. 2.05 ng/ml).

The sensitivity in detecting prostate cancer lesions was 77% (95% 69-84%) with [^{18}F]PSMA-1007 and 57% (95%CI 48-67%) with FCH. The positive predictive values were similar, at 0.95 and 0.97 for [^{18}F]PSMA-1007 and FCH, respectively.
The proportion of patients with correct detection rate of prostate cancer lesions was analysed descriptively according to baseline PSA level (categories <0.5 ng/ml, 0.5 < 1.0 ng/ml; ≥1.0 ng/ml < 2.0 ng/ml, ≥ 2.0 ng/ml). For both study drugs, the proportion of patients for whom prostate cancer recurrence was correctly identified was higher when the category with higher PSA values was assessed, but for all subgroups examined, more patients were correctly identified using [^{18}F]PSMA-1007 than with FCH.

6.4 Safety

The safety population of study ABX-CT-301 included 195 patients who received at least one of both radiotracers. Median injected activity in study ABX-CT-301 was 322.5 MBq (range 134.1-461.5).
Adverse events (AE) as reported in the safety follow-up period (24h after the second PET examination) were observed in 2.0% of patients with [^{18}F]PSMA-1007 injected first and in 0.5% of patients with FCH injected first. The AEs by preferred term were toothache, diarrhoea, chest discomfort and arterial hypertension in the [^{18}F]PSMA-1007 first group (in n=1 patient each) and shoulder pain in the FCH first group.
No serious adverse events or events of death occurred during the safety follow-up period.

In addition, the Applicant provided an overview of literature reports on the clinical use of [^{18}F]PSMA-1007. safety information was available for 198 subjects (195 patients, 3 healthy volunteers) in a total of 1093 subjects. No adverse events or other drug-related symptoms were reported.

6.5 Final clinical benefit risk assessment

Based on the efficacy and safety data provided, the benefit risk balance is considered positive for the visualisation of PSMA-positive lesions in adult patients with prostate cancer.

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 SWAN-PSMA-1007 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.

SWAN-PSMA-1007

▼ 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 the "Undesirable effects" section for advice on the reporting of adverse reactions.

Composition

Active substances

[^{18}F]PSMA-1007; (PSMA = prostate-specific membrane antigen), 222 MBq/mL

Synonym: ([^{18}F] Fluoro-Glu-NH-CO-NH-Lys-2-Nal-Amb-Glu-Glu-FNA)

Excipients

1 mL solution for injection in water for injections contains:

- Sodium chloride 6.00 mg (equivalent to 2.1 mg sodium)
- Sodium ascorbate 20 mg (equivalent to 2.3 mg sodium)
- Disodium phosphate (equivalent to 0.7 mg phosphate) 0.86 mg (equivalent to 0.2 mg sodium)
- Potassium dihydrogen phosphate (equivalent to 0.1 mg phosphate) 0.15 mg (equivalent to 0.0 mg potassium)
- Potassium chloride 0.15 mg
- Ethanol 0.075 mL (60 mg)

Specifications:

Radionuclide purity: [^{18}F] fluorine ≥ 99.9%

Radiochemical purity: [^{18}F]PSMA-1007 ≥ 93% (HPLC, at calibration), [^{18}F]PSMA-1007 ≥ 91% (HPLC, at the end of the shelf life)

Free [^{18}F] fluoride ≤ 5% (TLC)

PSMA-1007: 0.01 mg/mL

Other impurities (total): ≤ 0.05 mg/mL

Pharmaceutical form and active substance quantity per unit

SWAN-PSMA-1007 is a ready-to-use radiodiagnostic agent for direct administration. SWAN-PSMA-1007 is a clear, colourless solution for IV injection for multiple use. 1 mL solution for injection contains 222 MBq/mL of the active substance [^{18}F]PSMA-1007 at the date and time of calibration. One vial contains between 1 mL and 10 mL of solution for injection. The activity of each vial at the time of calibration thus falls between 222 MBq and 2,222 MBq.

Indications/Uses

SWAN-PSMA-1007 ([^{18}F]PSMA-1007) is a radiodiagnostic agent indicated for the imaging detection of prostate-specific membrane antigen (PSMA)-positive lesions with positron emission tomography (PET) in adult patients with prostate cancer.

Dosage/Administration

This medicinal product is intended to be used exclusively in institutions authorised to use radionuclides.

Radiopharmaceuticals must be administered by or under the supervision of qualified and appropriately trained healthcare professionals who know how to use and handle radionuclides safely, whose experience and training have been recognised by the relevant state authorities competent to issue authorisations for the use of radionuclides.

Usual dosage

The maximum volume of SWAN-PSMA-1007 to be injected is 10 mL (max. 10 µg/mL F-18-PSMA-1007). The injected dose of max. 100 µg F-18-PSMA-1007 falls under the "micro-dosing" category of ICH GUIDANCE M3-R2, 2009. The radioactivity per injected dose is 2-4 MBq/kg body weight, depending on the imaging protocol and equipment used, up to a maximum of 360 MBq.

Special dosage instructions

Patients with hepatic disorders

The use of PSMA-1007 has not been investigated in patients with hepatic disorders. Due to the delayed biliary excretion, there is a prolonged and non-specific distribution through the body, which may result in a poor tumour to background ratio in the uptake process which can in turn impair the certainty of the diagnosis. In patients with hepatic disorders, an increase in the effective dose is possible.

Patients with renal disorders

The use of PSMA-1007 has not been investigated in patients with renal disorders.
In patients with renal disorders, no adjustment of the injected activity is necessary compared to the recommended activity in people with normal renal function, as the urinary excretion of PSMA-1007 in healthy individuals is very low and the radiation exposure hardly influenced.

Elderly patients

No age-related dose adjustment is necessary.

Children and adolescents

SWAN-PSMA-1007 is not authorised for use in the paediatric population. The safety and efficacy of ^{18}F-PSMA-1007 have not been investigated in children and adolescents under 18 years.

Mode of administration

SWAN-PSMA-1007 is intended for IV use. The amount of SWAN-PSMA-1007 activity to be administered must be measured with an activimeter (dose calibrator) immediately prior to the injection.
SWAN-PSMA-1007 must not be diluted, except in isotonic sodium chloride solution for injection.
The medicinal product must be administered by the IV route, followed by a flush of approx. 10 mL isotonic sodium chloride solution for injection to ensure complete administration of the dose. For injection volumes below 1 mL, syringes of an appropriate size (1 mL) must be used. After the injection, the 1 mL syringe must then be refilled with 0.9% sodium chloride solution and administered again, to ensure that the entire quantity of activity was injected.
SWAN-PSMA-1007 must strictly be injected intravenously, to avoid radiation exposure due to local extravasation as well as artefacts in the images.

Image acquisition

The patient must be in the supine position, where possible with their arms above their head. To correct for attenuation and confirm the anatomical location of the lesion visualised on the PET image, a CT or MRI scan must also be performed. The PET scan should be initiated 90 to 120 minutes after the end of the injection. Image acquisition from the mid-thigh to skull base is recommended.

Image interpretation

The images acquired with [^{18}F]PSMA-1007 must be assessed by a nuclear medicine specialist registered with the FMH (Swiss medical association) or equivalent state-recognised body who is appropriately trained in PET scans in the field of prostate cancer.

The PET images acquired with [^{18}F]PSMA-1007 must be interpreted visually. Tumour tissue at the typical sites of prostate cancer recurrence can be suspected if higher uptake of [^{18}F]PSMA-1007 is observed at these sites compared to background activity; this suspicion is then to be further investigated using information from the corresponding CT and/or MRI scans. In the process, the known physiological fixation of PSMA and PSMA-1007 in specific targeting tracers should be taken into account.
With [^{18}F]PSMA-1007, prostate cancer recurrence has been detected in the prostate bed, regional and distant lymph nodes, bone, soft tissue, and visceral organs.
The significance of quantitative/semiquantitative measurement of [^{18}F]PSMA-1007 uptake to aid image interpretation has not been assessed.
No contrast agent is needed to assess PET/CT or PET/MRI images with [^{18}F]PSMA-1007.

Radiation exposure
The estimated radiation doses absorbed by adult patients following intravenous injection of [^{18}F]PSMA-1007 are listed in the tables below. Values were calculated from human distribution data using the software OLINDA/EXM (Organ Level Dose Assessment/Exponential Modeling) version 2.1. The effective dose was calculated according to the organ weighting factors defined in the International Commission on Radiological Protection publication 103 (ICRP-103).

Estimated doses of radiation absorbed by prostate cancer patients following administration of [^{18}F]PSMA-1007.

Organ	Dose absorbed per unit of activity administered (mGy/MBq)
Brain	0.0030
Eyes	0.0072
Testes	0.0074
Osteogenic cells	0.0101
Muscle	0.0103
Total body	0.0103
Thymus	0.0106
Red marrow	0.0121
Rectum	0.0145
Lungs	0.0147
Thyroid	0.0151
Stomach	0.0170
Upper colon	0.0176
Oesophagus	0.0187
Urinary bladder wall	0.0212

Lower colon	0.0239
Heart wall	0.0259
Small intestine	0.0334
Adrenals	0.0349
Salivary glands	0.0642
Pancreas	0.0677
Spleen	0.0851
Liver	0.0883
Kidneys	0.1030
Gallbladder wall	0.1400
Effective dose	
Effective dose (mSv/MBq) (ICRP-103)	**0.0191**

The effective dose following administration of an activity of 280 MBq (in an adult weighing 70 kg) is approx. 5.3 mSv.
The effective dose following administration of the recommended maximum activity of 360 MBq is approx. 6.9 mSv.
At an activity of 280 MBq, the radiation dose absorbed by the critical organs is 39 mGy for the gallbladder, 29 mGy for the kidneys, and 25 mGy for the liver.

Contraindications

Hypersensitivity to the active substance or any of the excipients.

Warnings and precautions

Restrictions on use
Interactions between new-generation hormone therapies and PSMA-PET have been described in the literature and should be taken into account accordingly when assessing the PSMA PET/CT images (see "Interactions").

Individual benefit/risk assessment
For each patient, the radiation exposure must be justified by the likely diagnostic benefit. The administered activity must always be kept as low as possible and should not be set higher than what is needed to obtain the diagnostic information.

Risk of interpretation errors
When interpreting [^{18}F]PSMA-1007 PET images, errors can occur. [^{18}F]PSMA-1007 uptake is not specific to prostate cancer, and false positive findings in the event of other types of cancer, prostatitis, or benign prostatic hyperplasia therefore cannot be ruled out.

Further false positive findings have also been described with active inflammatory processes in the lymph nodes, benign thyroid conditions, benign bone diseases, hepatitis, and healing rib fractures. Where applicable, further investigations should be considered, such as a histopathology assessment of the suspected lesion.

Radiation risk
Radioactive products must be handled with the utmost care and strict radiation protection measures in order to keep exposure to radiation as low as possible for both patients and medical personnel. [^{18}F]PSMA-1007 contributes to the total long-term cumulative radiation exposure of patients. Long-term cumulative exposure to radiation is associated with an increased risk of cancer. Each use of radiopharmaceuticals in patients falls under the exclusive competency and responsibility of the state-authorised nuclear medicine specialist. In all cases, administration must take place in compliance with radiation protection rules.

After the procedure
Patients are advised to avoid close contact with children and pregnant women for the first 12 hours after the injection.

This medicinal product contains 46 mg sodium (main component of cooking/table salt) in each 10 mL (maximum dose). This is equivalent to 2.3% of the recommended maximum daily dietary intake of sodium for an adult.

This medicinal product contains 600 mg alcohol (ethanol) in each 10 mL (maximum dose). The amount in 10 mL (maximum dose) of this medicinal product is equivalent to less than 20 mL beer or 10 mL wine. The small amount of alcohol in this medicinal product will not have any noticeable effects.

Interactions

The interaction potential of SWAN-PSMA-1007 has not been tested in *in vitro* or clinical studies. As SWAN-PSMA-1007 is primarily eliminated via the hepatobiliary route, interactions with liver enzymes and/or drug transporters may be possible. The clinical significance of this is not known.

Interactions between new-generation hormone therapies and PSMA-PET have been described in the literature and should be taken into account accordingly when assessing the PSMA PET/CT images.

Pregnancy, lactation

SWAN-PSMA-1007 is not indicated for use in women.
No animal studies have been performed to assess the reproductive toxicity of [^{18}F]PSMA-1007.

Lactation
SWAN-PSMA-1007 is not indicated for use in women.

Fertility
No fertility studies have been performed.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Undesirable effects

At the concentrations of [^{18}F]PSMA-1007 recommended for diagnostic use, no pharmacological effects are expected. To date, no adverse reactions have been observed following the use of [^{18}F]PSMA-1007 in clinical studies. The main safety data are derived from 190 patients (see also "Clinical efficacy").

Ionising radiation can lead to cancer and the development of hereditary defects. The greatest risk of the use of SWAN-PSMA-1007 in patients is therefore associated with radiation exposure.
A maximum of 10 mL solution for injection is administered via slow IV injection; this contains a maximum of 100 µg [^{18}F]PSMA-1007. The target radioactivity of [^{18}F]PSMA-1007 is 250 ± 50 MBq per injection, depending on body weight. The effective dose of a typical administered activity of 280 MBq [^{18}F]PSMA-1007 is 5.3 mSv (or a maximum of 7.9 mSv for 360 MBq). The effective dose of the supporting CT scan should be kept as low as possible.
As with other solutions for injection, allergic and anaphylactic reactions cannot be ruled out, although none have been reported to date.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

The radioactivity of SWAN-PSMA-1007 must be measured in an activimeter in order to determine the dose prior to administration.

The active substance is administered in very low quantities for diagnostic purposes, which should not result in an overdose in the pharmacological sense.

Management

Hydration adjusted to the risk profile can increase the clearance of the radiopharmaceutical. It may be

helpful to estimate the effective dose that was administered.

Properties/Effects

ATC code

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals; ATC code: V09IX17

Mechanism of action

[^{18}F]PSMA-1007 is a synthetic peptidomimetic which contains the prostate-specific membrane antigen (PSMA) pharmacophore Glu-NH-CO-NH-Lys. It binds with high affinity to the PSMA enzymatic site, which is over-expressed in most prostate cancer cells and is internalised after binding. Due to internalisation, enhanced accumulation of [^{18}F]PSMA-1007 in prostate cancer cells occurs.

Pharmacodynamics

At molar concentrations corresponding to the recommended activities for diagnostic investigations, [^{18}F]PSMA-1007 does not appear to have any pharmacodynamic activity.

Clinical efficacy

The main efficacy data stem from 190 patients assessed at six different trial sites in France as part of the study ABX-CT-301. These patients were adult and elderly men who had had initial curative therapy of locally limited prostate cancer and were suspected of having a recurrence due to increased serum PSA concentrations.

In this comparator study, a PET scan with [^{18}F]PSMA-1007 (SWAN-PSMA-1007) was compared against a PET scan with fluorocholine (^{18}F).

The PET/CT images produced for each patient using both radiopharmaceuticals were assessed by blinded external reviewers, and the observed results were compared using a combined standard of reference (SOR) for which the extent of the tumour was determined by a group of experts who were blinded with respect to the two PET/CT scans.

The diagnostic performance of PET/CT imaging with [^{18}F]PSMA-1007 and fluorocholine (^{18}F) was determined using the correct detection rate (observed results consistent with the SOR) as shown in Table 1.

The total detection rate for all reviewers was 77% for [^{18}F]PSMA-1007 and 57% for fluorocholine (^{18}F); the difference was statistically significant. The detection rates stratified by serum PSA concentrations are also shown in Table 1.

Table 1: Correct detection rate of prostate cancer lesions, blinded assessment using SOR as a reference, at the patient level.

	N	[^{18}F]PSMA-1007 (SWAN-PSMA-1007)	Fluorocholine (^{18}F)	Odds Ratio [^{18}F]PSMA-1007/ fluorocholine (^{18}F)	*p* value*
Total detection rate	179	77.0%	56.5%	2.61	< 0.0001
Detection rate per serum PSA concentration					
PSA < 0.5 ng/mL	43	56.6%	38.8%	2.10	
0.5 ≤ PSA < 1.0 ng/mL	25	82.7%	42.7%	6.88	
1.0 ≤ PSA < 2.0 ng/mL	33	80.8%	49.5%	4.31	
PSA ≥ 2.0 ng/mL	78	84.6%	73.5%	2.01	

*Chi-square test based on generalised estimated equations

Pharmacokinetics

Absorption

[^{18}F]PSMA-1007 is administered intravenously.

Distribution

[^{18}F]PSMA-1007 is distributed immediately following intravenous administration. In healthy subjects, 76%, 22%, 12%, and 8% of the injected activity was detected in the blood compartment 2 minutes, 1 hour, 2 hours and 3 hours after injection, respectively.
[^{18}F]PSMA-1007 is preferentially taken up in prostate cancer cells and less in the healthy surrounding tissue. One hour after the injection, cancer lesions are visible; uptake increases for up to 3 hours after the injection. Median SUV_{max} in prostate cancer lesions in patients with biochemical recurrence is between 4 and 40.
In non-target organs, the highest uptake of [^{18}F]PSMA-1007 has been observed in the kidneys, salivary glands, lacrimal glands, liver, spleen, and gallbladder up to 3 hours after the injection (median SUV_{mean} approx. 12-30). Activity in the brain is negligible.

Metabolism

The metabolism of [^{18}F]PSMA-1007 has not been investigated.

Elimination

Hepatobiliary excretion is assumed to be the major elimination pathway of [^{18}F]PSMA-1007. However, it has not been quantitatively characterised, and the possible enzymes and drug transporters involved are not known.
In a study with 3 healthy volunteers, urinary elimination was minimal: within 6 hours of the injection, a mean of 2.4% of the administered radioactivity was excreted in the urine.

Kinetics in specific patient groups

Hepatic insufficiency
The pharmacokinetics and biodistribution of [^{18}F]PSMA-1007 have not been investigated in patients with hepatic impairment. As [^{18}F]PSMA-1007 is likely primarily excreted via the hepatobiliary route, increased exposure is to be expected in patients with hepatic impairment.

Renal insufficiency
The pharmacokinetics and biodistribution of [^{18}F]PSMA-1007 have not been investigated in patients with renal impairment. Renal impairment is unlikely to influence in the pharmacokinetics of [^{18}F]PSMA-1007 to a clinically relevant extent.

Other information
The influence of ethnicity or body weight on the pharmacokinetics and biodistribution of [^{18}F]PSMA-1007 has not been investigated.

Preclinical data

Safety pharmacology

[^{18}F]PSMA-1007 has been investigated in safety pharmacology and single-dose toxicity studies. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and single-dose toxicity.

Carcinogenicity and reproductive toxicity

No studies on the mutagenic or carcinogenic potential or the reproductive toxicity of [^{18}F]PSMA-1007 have been performed.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with any other medicinal products except for 0.9% sodium chloride solution.

Effects on diagnostic methods

See section "Restrictions on use".

Shelf life

Up to 10 hours from the time of production (end of synthesis). Do not use this medicine after the expiry time on the data of production marked as "EXP" on the pack.

Special precautions for storage

Until first use, this radiopharmaceutical can be stored upright at room temperature (15-25 °C) in the original container with a lead or tungsten cover.

Instructions for handling

Preparation
Until first use, this radiopharmaceutical can be stored upright at room temperature (15-25 °C) in the original container with a lead or tungsten cover. The pack must be checked before use and the activity measured with an activimeter (dose calibrator). The content should be withdrawn under aseptic conditions. The vial must not be opened until the stopper has been disinfected, and the solution must be withdrawn using a single-use syringe with a suitable protective shield and sterile single-use needle, or with an automated use system released for this purpose. The medicinal product must not be used if the integrity of the vial cannot be ensured.
Quality control
The solution must be visually inspected before use. Only clear solutions with no visible particulate matter can be used.

Legal requirements

When using radioactive substances in humans, the Swiss Radiological Protection Ordinance must be complied with. To handle radioactive substances, an authorisation from the Swiss Federal Office of Public Health is required. When handling radioactive substances and disposing of any radioactive waste, the safety precautions set out in the above ordinance must be followed to avoid unnecessarily exposing patients and medical personnel to radiation. Any unused radioactive solutions and objects contaminated by them must be stored in a decay facility designated for this purpose until the activity has fallen to the clearance limit for the radionuclide.

Authorisation number

67370

Packaging

15 mL multidose glass vial with a stopper and aluminium seal.
Depending on the needs of the user, each multidose vial contains 1.0 mL to 10.0 mL of solution, equivalent to an activity of 222 to 2,222 MBq at the time of calibration.
Pack size: one vial.
Dispensing category: A

Marketing authorisation holder

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CH-3010 Bern
Switzerland

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