swissmedic

Date: 24 September 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Pylclari

International non-proprietary name:	piflufolastat (^{18}F)
Pharmaceutical form:	solution for injection
Dosage strength(s):	1500 MBq/ml and 1000 MBq/ml
Route(s) of administration:	intravenous
Marketing authorisation holder:	b.e.imaging.ag
Marketing authorisation no.:	69775
Decision and decision date:	approved on 25 April 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
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
Ki	Inhibitory constant
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
PCa	Prostate Cancer
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
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 piflufolastat (^{18}F) 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.
Pylclari is indicated for the detection of prostate-specific membrane antigen (PSMA) positive lesions with positron emission tomography (PET) in adults with prostate cancer (PCa) in the following clinical settings:
• Primary staging of patients with high-risk PCa prior to initial curative therapy,
• To localise recurrence of PCa in patients with a suspected recurrence based on increasing serum prostate-specific antigen (PSA) levels after primary treatment with curative intent.

2.2.2 Approved indication

This medicinal product is for diagnostic use only.
Pylclari is indicated for the detection of prostate-specific membrane antigen (PSMA) positive lesions with positron emission tomography (PET) in adults with prostate cancer (PCa) in the following clinical settings:

- Primary staging of patients with high-risk PCa prior to initial curative therapy,
- To localise recurrence of PCa in patients with a suspected recurrence based on increasing serum prostate-specific antigen (PSA) levels after primary treatment with curative intent.

2.2.3 Requested dosage

Summary of the requested standard dosage:
The standard dose for adults is 3 - 5 MBq/kg body weight, whereby the maximum dose should not exceed 360 MBq and the minimum dose should not fall below 190 MBq.
The medicinal product has not been tested for children and adolescents, nor for patients with liver dysfunction. Dose adjustment must be carefully considered for patients with renal impairment.
A table of radiation exposure for the organs is available.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	22 January 2024
Formal control completed	09 February 2024
List of Questions (LoQ)	28 June 2024
Response to LoQ	20 September 2024
Preliminary decision	20 December 2024
Response to preliminary decision	07 February 2025
Final decision	25 April 2025
Decision	approval

3 Medical context

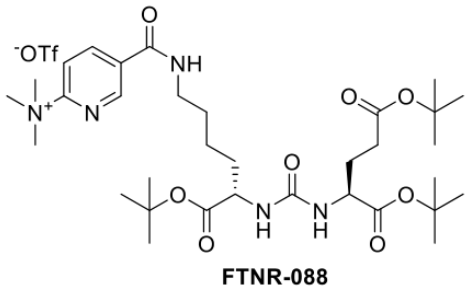
Prostate cancer is the second leading cause of cancer-related death among men in the US and the third leading cause of cancer-related death in Europe.
Diagnostic work-up of prostate cancer includes PSA testing, digital rectal palpation, transrectal ultrasound (TRUS), prostate biopsy, and histopathological examination. For unfavourable intermediate, high-risk, and very high-risk disease, bone and soft tissue imaging is recommended according to the NCCN guidelines (version 4.2024). 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 work-up for progression.
PSMA is a transmembrane protein with an extracellular binding site. PSMA tissue expression is high on the cell surface of prostatic tissues including prostate cancer, and most adenocarcinomas of the prostate express high levels of PSMA in primary and metastatic lesions. However, despite the name, PSMA is not specific to prostate tissue and the PSMA protein can be found in low concentrations in many other organs.
[^{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.

4 Quality aspects

4.1 Drug substance

Non-radioactive precursor

INN:	not yet assigned
Company Code:	FTNR-088
Chemical name:	5-(((S)-6-(tert-butoxy)-5-(3-((S)-1,5-di-tert-butoxy-1,5-dioxopentan-2-yl) ureido)-6-oxohexyl)carbamoyl)-N,N,N-trimethylpyridin-2-aminium trifluoromethanesulfonate
Molecular formula:	$C_{34}H_{56}F_3N_5O_{11}S$
Molecular mass:	650.84 g/mol
Molecular structure:	



FTNR-088

TfO^- - triflate [trifluoromethanesulfonate]

Physicochemical properties:
White to slightly yellow solid. Soluble in organic solvents such as dichloromethane, ethanol, methanol and acetonitrile.

Synthesis:
The drug substance precursor is obtained by a convergent synthetic route using conventional liquid phase synthesis. The different arms of the route are combined in the final step, where the final drug

substance precursor is isolated and purified by crystallisation. The process includes several intermediates.

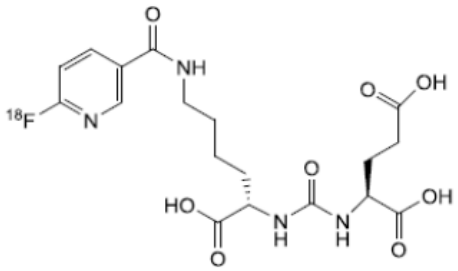
Specification:
In order to ensure a consistent quality of the drug substance precursor, the specifications include all relevant test parameters as recommended by the relevant ICH guidelines and compliant with the current Ph.Eur. The analytical methods are adequately described, and the non-compendial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

Stability:
Appropriate stability data have been presented both for the “bulk” and “commercial” presentations. Based on the results, satisfactory re-test periods have been established when stored at the recommended conditions (–20°C ± 5°C for the “bulk” presentation (protected from light); +25°C ± 2°C for the “commercial” presentation).

Quality Conclusions: Swissmedic
Satisfactory and consistent quality of the drug substance precursor has been demonstrated.

Drug substance (radioactive)

INN:	Piflufolastat (^{18}F)
Chemical name:	2-(3-(1-carboxy-5-[(6-[^{18}F]fluoropyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid.
Molecular formula:	$C_{18}H_{23}{}^{18}FN_4O_8$
Molecular mass:	441.4 g/mol
Molecular structure:	



Physicochemical properties:
Piflufolastat (^{18}F) is a radioactive substance with a half-life of F-18 of approximately 110 minutes. The decay mode is mainly β^+.

Synthesis:
The drug substance is manufactured in a radiosynthesis from non-radioactive precursor material, FTNR-088, 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 piflufolastat (^{18}F) and formulation of its bulk solution are performed using an automated synthesiser, disposable cassette and commercial reagent kit. It starts with a nucleophilic substitution in which the precursor FTNR-088 reacts with [^{18}F]fluoride to the O-tert-butylated piflufolastat (^{18}F). The tert-butylated protecting groups are removed with phosphoric acid, which is partially neutralised at the end of the reaction with sodium hydroxide. The crude piflufolastat (^{18}F) is purified by a semi-preparative HPLC and then eluted with ethanol, followed by a sodium ascorbate solution in saline to produce the bulk formulated drug product.

Specification and Stability: see next paragraph.

4.2 Drug product

Description and composition:
The diagnostic radiopharmaceutical preparation Pylclari (named in this chapter according to Module 3.2.P. [^{18}F]-DCFPyL), a solution for injection, is presented in a multi-dose vial containing between 0.5 ml and 10 ml, with a radioactive concentration of 1000 MBq/ml or 1500 MBq/ml.

Pharmaceutical development:
The initial synthesis of [^{18}F]-DCFPyL was performed at Johns Hopkins University. Subsequently, the drug product underwent improvements throughout the pharmaceutical development process. A single precursor, FTNR-088, was employed for radiofluorination. The synthesis and radiolabelling process was optimised through the implementation of two radiochemistry modules. The final formulation is designed to stabilise the product, ensuring its effectiveness and long-term stability.

Manufacture:
The manufacturing process for the piflufolastat (^{18}F) drug substance, formulation, sterile filtration, and dispensing of [^{18}F]-DCFPyL (solution for injection, drug product) involves the use of a bulk solution directly transferred from the synthesis unit. At no stage is the active drug substance isolated, stored, or released. All development steps within the manufacturing process have been fully detailed, and the required information regarding the batch formula has been provided.

Specification:
Specifications with acceptance criteria have been defined. Specifications for the [^{18}F]-DCFPyL solution for injection include diverse tests and acceptance criteria, for example the appearance of the solution, diverse identity tests, physiologically relevant tests (including sterility, bacterial endotoxins, and pH), chemical purity tests, radiochemical purity tests. These criteria ensure the quality and compliance of the [^{18}F]-DCFPyL solution for injection.

Analytical Methods:
Analytical test procedures are described and validated; impurity determination is described. Chromatograms are provided.

Container Closure System:
The commercial packaging of [^{18}F]-DCFPyL, solution for injection, consists of 15 ml Type I glass vials sealed with a chlorobutyl rubber stopper and an aluminium crimp seal. For radiation protection, a lead or tungsten container serves as the functional secondary packaging. This shield is enclosed within a transport case that meets the standards for Type A packaging.

Stability:
The chemical and physical stability has been demonstrated for 11 hours at 40°C. The product should not be stored above 30°C and must be used within 11 hours after labelling. After dilution, it can be stored for a maximum of 4 hours, provided the expiry time is not exceeded.

4.3 Quality conclusions: Expert Commission for Radiopharmaceuticals

The product seems satisfactory and consistent in the quality of its drug substance and drug product.

5 Nonclinical aspects

5.1 Pharmacology

Primary pharmacology was investigated in enzyme inhibition and saturation assays, as well as in small animal PET imaging studies. Piflufolastat bound competitively to PSMA-expressing LNCaP cells with a Ki of 1.1 nM. [^{18}F]-piflufolastat exhibited high affinity binding (K_d = 0.83 ± 0.04 nM) and high specific binding (85–98 %) to PSMA in *in vitro* saturation binding studies.
[^{18}F]-piflufolastat showed PSMA-dependent uptake within PSMA-positive PC3 PIP xenografts and demonstrated significant uptake and retention in the PSMA-positive tumour. These data suggested that the uptake of [^{18}F]-piflufolastat is PSMA-specific and provided adequate pharmacology support for the use of [^{18}F]-piflufolastat as a diagnostic agent for the detection of PCa.
[^{18}F]-piflufolastat is a microdose diagnostic agent which is administered at a low mass dose of ≤ 40 µg. It is highly selective for PSMA. The selectivity and the very low chemical mass render any meaningful interaction with off target receptors, transporter, and ion channels, including the hERG potassium channel, highly unlikely. Thus, the interaction of [^{18}F]-piflufolastat with PSMA is unlikely to result in any clinically significant pharmacological or toxicological concern.

5.2 Pharmacokinetics

[^{18}F]-piflufolastat is a microdose radiopharmaceutical diagnostic agent; the maximum chemical mass of Piflufolastat associated with the proposed recommended dose of 330 MBq (9 mCi) is ≤ 40 µg, which translates to a maximum theoretical instantaneous blood concentration of ≤ 18 nM. The extremely low mass dose is highly unlikely to inhibit or induce any of the metabolising enzymes. [^{18}F]-piflufolastat confirmed very high metabolic stability of the radiotracer in normal healthy mice. Furthermore, since [^{18}F]-piflufolastat does not undergo meaningful metabolism following IV administration in humans (Szabo *et al*., 2015[1]), its pharmacokinetics would not be affected by concomitant inducers and/or inhibitors of metabolising enzymes. Taken together, the potential for meaningful [^{18}F]-piflufolastat pharmacokinetic drug interactions is negligible.

5.3 Toxicology

In an extended single dose toxicity study in rats, which also included histopathological evaluation, there were no adverse effects in doses up to 0.5 mg/kg piflufolastat. This dose is over 875-fold higher than the clinical dose of 40 µg/patient (or 0.5714 µg/kg for a reference body weight of 70 kg).
[^{18}F]-piflufolastat was not genotoxic under the conditions investigated.

5.4 Nonclinical conclusions

In conclusion, the nonclinical profiles of [^{18}F]-piflufolastat is considered to be sufficiently characterised. The submitted nonclinical data support the use of [^{18}F]-piflufolastat as a PET tracer for imaging prostate cancer. The relevant information has been included in the Information for healthcare professionals.

[1] Szabo Z, Mena E, Rowe SP, et al. initial evaluation of [^{18}F]DCFPyL for prostate-specific membrane antigen (PSMA)-targeted PET imaging of prostate cancer. Mol Imaging Biol. 2015;17(4):565-574.

6 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign authorities EMA and FDA. The clinical aspects in this SwissPAR refer to the publicly available assessment report on Pylclari, EMA/CHMP/279917/2023 dated 28.07.2023 and issued by the EMA, and the publicly available assessment report on Pylarify dated 26.05.2021 and issued by the FDA.

6.1 Final clinical benefit risk assessment

The benefit-risk assessment is positive for the primary staging of patients with prostate cancer at high-risk for metastases and for the staging of patients with prostate cancer suffering a biochemical recurrence.

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 Pylclari 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.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section “Undesirable effects”.

Pylclari, solution for injection

Composition

Active substances

Pylclari 1 000 MBq/mL solution for injection

Each mL of solution contains 1 000 MBq of piflufolastat (^{18}F) at the date and time of calibration.

The total activity per vial ranges from 500 MBq to 10 000 MBq at the date and time of calibration.

Pylclari 1 500 MBq/mL solution for injection

Each mL of solution contains 1 500 MBq of piflufolastat (^{18}F) at the date and time of calibration.

The total activity per vial ranges from 750 MBq to 15 000 MBq at the date and time of calibration.

Fluorine (^{18}F) decays to stable oxygen (^{18}O) with a half-life of 110 minutes by emitting a positronic radiation of maximum energy of 634 keV, followed by photonic annihilation radiations of 511 keV.

Excipients

- Ethanolum
- Natrii chloridum 9 mg/ml (0,9 %) Injektionslösung
- Natrii ascorbas

Each ml of solution contains a maximum of 3,68 mg sodium and 90 mg ethanol.

Pharmaceutical form and active substance quantity per unit

Solution for injection.

Clear, colourless solution with a pH ranging from 4,5 to 7,5.

Indications/Uses

This medicinal product is for diagnostic use only.

Pylclari is indicated for the detection of prostate-specific membrane antigen (PSMA) positive lesions with positron emission tomography (PET) in adults with prostate cancer (PCa) in the following clinical settings:

- Primary staging of patients with high-risk PCa prior to initial curative therapy,
- To localize recurrence of PCa in patients with a suspected recurrence based on increasing serum prostate-specific antigen (PSA) levels after primary treatment with curative intent.

Dosage/Administration

This medicinal product is for use in designated nuclear medicine facilities only and should only be handled by authorised personnel.

Posology

The mean recommended activity of Pylclari is 4 MBq/kg of body weight and can vary from 3 to 5 MBq/kg of body weight depending on the PET equipment and acquisition mode used. The minimum activity should not fall below 190 MBq and the maximum activity should not exceed 360 MBq.

Renal impairment / Hepatic impairment

Pylclari has only been studied in patients with mild renal impairment. Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in patients with severe impaired renal function.

Pylclari has not been studied in patients with hepatic impairment.

Paediatric population

Pylclari is not approved for use in the paediatric population. The safety and efficacy of Pylclari in children and adolescents below 18 years of age have not been established.

Method of administration

It is administered by a single intravenous injection.

The application volume depends on the time interval between the initial calibration and the application time; it must be calculated with appropriate decay correction factors and measured with an activity meter prior to injection. The volume of solution to be administered can be 0,2 ml to 10 ml.
Care should be taken during injection to ensure that the radioactive material does not enter the surrounding tissue. If possible, inject via a pre-placed indwelling venous catheter. The ready-to-use medicinal product may be diluted with sodium chloride solution for injection (see section “Instructions for handling”).

Patient preparation

The patient should be well hydrated before the start of the examination and urged to void before the examination in order to reduce bladder activity and as often as possible during the first hours after the examination in order to reduce radiation exposure.
A diuretic expected to work within the admission period may be administered to better interpretation of piflufolastate (^{18}F) PET/CT as it results in lower activity retention in the ureters and bladder.

Image acquisition

It is recommended to position the patient supine with arms above the head. A non contrast-enhanced low-dose CT scan is performed from the vertex of the skull through mid-thigh for attenuation correction and anatomic correlation. The PET acquisition is performed from mid-thigh through the vertex of the skull, starting 90 to 120 minutes after tracer injection. It must include lower extremities if there is known or suspected disease. Image acquisition duration is 12 to 40 minutes depending on the type of PET cameras, number of bed positions (typically 6 to 8) and acquisition time per bed position (typically 2 minutes to 5 minutes). If the acquisition leads to indeterminate findings, and provided a sufficient activity remains for adequate counting statistics, late acquisitions can also be performed, thus reducing background activity.

Radiation exposure

Fluorine (^{18}F) has a half-life of 110 minutes and decomposes to stable oxygen (^{18}O) by emitting positron radiation with a maximum energy of 634 keV followed by photon radiation of 511 keV.
Pylclari exhibits biexponential behaviour in the blood, with the distribution half-life being 0,17 ± 0,044 hours and the elimination half-life being 3,47 ± 0,49 hours. Within 60 minutes of intravenous administration, it distributes to the kidneys (16,5% of administered activity), the liver (9,3%) and the lungs (2,9%).
Time-integrated activity in the initial tissue was obtained from longitudinal image data. Contours or Volumes of Interest (VOIs) were usually drawn around different organs containing activity, which were identified at each point in time on each image. The S value was determined by means of Monte-Carlo

simulation. The absorbed doses were calculated using the 3D-RD-S software. The resulting effective dose was calculated according to ICRP 110.

ORGAN	**ABSORBED DOSE PER UNIT ACTIVITY ADMINISTERED (mGy/MBq)**
Adrenals	0,0326
Bone surfaces	0,00662
Brain	0,00215
Breast	0,00767
Gallbladder wall	0,0255
Gastrointestinal tract	
Stomac wall	0,0127
Small Intestine wall	0,0101
Colon wall	
Upper intestinal wall	0,0125
Lower intestinal wall	0,0101
Heart wall	0,0178
Kidneys	0,124
Liver	0,0388
Lungs	0,0121
Mjuscles	0,00714
Pancreas	0,0183
Red marrow	0,00851
Skin	0,0054
Spleen	0,0283
Testes	0,00638
Thymus	0,00769
Thyroid	0,00687
Urinary bladder wall	0,00712
Effective dose (mSv/MBq)	**0,0121**

The effective dose resulting from the administration of a maximal recommended activity of 360 MBq for an adult weighing 70 kg is about 4,4 mSv.
For an administered activity of 360 MBq, the typical radiation doses to the critical organs (kidneys, liver and spleen) are 44,6 mGy, 14 mGy and 10,2 mGy respectively.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in the section “Excipients”.

Warnings and precautions

Limitations of applicability

Interactions between newer-generation antihormonal therapy and PSMA-PET have been described in the literature and should be taken into account when reviewing the PSMA-PET/CT (see “Interactions”).

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

Radioactive preparations should be handled with special care and under strict radiation protection measures in order to keep the radiation exposure to patients and staff as low as possible.
Exposure to ionising radiation is associated with cancer induction and a potential to develop hereditary damage. Any use of radiopharmaceuticals on patients is exclusively the competence and responsibility of nuclear medicine physicians approved by the authorities. In any case, administration must be carried out under the rules of radiation protection.

Renal impairment

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

After the procedure

Close contact with infants and pregnant women should be restricted during the initial 12 hours following the injection.

Interpretation of Pylclari images

The recommended method for PET images interpretation with Pylclari PET/CT is the visual interpretation.
Lesions should be considered suspicious if uptake is greater than physiologic uptake in that tissue or greater than adjacent background if no physiologic uptake is expected.

Pylclari accumulates in normal tissue where the density of PSMA is high including the lacrimal glands, salivary glands, liver, spleen, and kidneys. Normal organs demonstrate significant variability in the uptake of piflufolastat (^{18}F); however, the impact of tumor burden on normal uptake is minimal and unlikely to be clinically significant. The expression of PSMA can predominantly be found in prostate cancer, but can also be observed in other neoplasms (e.g. renal cell carcinoma, hepatocarcinoma, breast cancer, lung cancer and other malignancies) or non-malignant conditions (e.g hemangioma, ganglia, since they can mimic lymph nodes, benign bone disease as Paget's disease, or pulmonary sarcoidosis/granulomatosis).

The images should only be interpreted by nuclear medicine specialists who are trained in the interpretation of PET images with Pylclari.

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

Pylclari was not studied for detection of distant metastases in primary staging.

The performance of Pylclari for imaging of patients with biochemical evidence of recurrence of prostate cancer seems to be affected by serum PSA levels (see section "Pharmacokinetics"). The performance of Pylclari for imaging of metastatic pelvic lymph nodes prior to initial definitive therapy seems to be affected by risk factors such as Gleason score.

Small lymph nodes metastases, or any lesion under spatial resolution of PET (= 5 mm) may be missed by Pylclari PET/CT.

To date no outcome data exist to support subsequent management of patients based on PSMA-PET in the primary staging. Therefore, treatment should not be changed based on Pylclari PET/CT findings only.

Specific warnings

This medicinal product contains a maximum of 3,68 mg to 36,8 mg sodium per dose, depending on the dose administered. This represents 0,18% to 1,84% of the WHO recommended maximum daily intake of 2 g for an adult.

This medicinal product contains up to 900 mg of alcohol (ethanol) in each administration which is equivalent to 90 mg per mL. The amount in 10 mL of this medicinal product is equivalent to less than 23 mL of beer or 11 mL of wine.
The small amount of alcohol in this medicinal product will not have any noticeable effects.

Interactions

No interaction studies have been performed.

Androgen deprivation therapy (ADT) and other therapies targeting the androgen pathway, such as androgen receptor antagonists, may result in changes in uptake of Pylclari in prostate cancer.
The effect of these therapies on performance of Pylclari PET has not been established.

Chronic treatment with diuretics does not seem to have any interference with Pylclari for interpretation of images.

Pregnancy, lactation

Pregnancy

Pylclari is not intended for use in women.

No animal studies have been performed to investigate Pylclari with respect to reproductive toxicity.

Breast-feeding

Pylclari is not intended for use in women.

Fertility

No studies on fertility have been performed.

Effects on ability to drive and use machines

The effect of Pylclari on the ability to drive or use machines has not been studied.

Undesirable effects

Zusammenfassung des Sicherheitsprofils

The overall safety profile is based on data from its administration to 797 patients from three clinical studies and spontaneous reporting. In the clinical studies, each patient received a single administration with a median administered activity of 330 MBq.

The most common adverse events were headache (1,4%), dysgeusia (1,0%) and fatigue (0,5%). Serious drug-related adverse events have been reported with hypersensitivity, headache and paraesthesia. These events were singular and reversible.

Adverse reactions have been reported during clinical development and are listed below by MedDRA body system organ class.

Tabulated list of adverse reactions

The frequencies of adverse reactions are defined as follows: Very common (≥1/10), common (≥1/100 to <1/10), Uncommon (≥1/1 000 to <1/100), Rare (≥1/10 000 to <1/1 000), Very rare (<1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions observed with Pylclari

MedDRA body system organ class	Adverse reactions	Frequency
Immune system disorders	Hypersensitivity	Uncommon
Metabolism and nutrition disorders	Dehydration	Uncommon
Psychiatric disorders	Disorientation	Uncommon
Nervous system disorders	Syncope	Not known*
	Dysgeusia	Common
	Headache	
	Dizziness	Uncommon
	Hyperaesthesia	
	Migraine	
Eye disorders	Visual field defect	Uncommon
Ear and labyrinth disorders	Vertigo	Uncommon
Gastrointestinal disorders	Nausea	Not known*
	Vomiting	
Skin and subcutaneous tissue disorders	Dry skin	Uncommon
	Rash	
Musculoskeletal and connective tissue disorders	Arthralgia	Uncommon
	Muscular weakness	
	Pain in extremity	
Renal and urinary disorders	Dysuria	Uncommon
General disorders and administration site conditions	Fatigue	Uncommon
	Chest discomfort	Uncommon
	Application site rash	
	Feeling abnormal	
	Injection site pain	

*Adverse reactions derived from spontaneous reporting with a not known frequency.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the 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 maximum amount of Pylclari injection that can be safely administered to humans has not been determined.

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

Properties/Effects

ATC code

V09IX16.

Mechanism of action

Prostate-Specific Membrane Antigen (PSMA), is a trans-membrane glycoprotein primarily expressed in normal human prostate epithelium at low levels, but may be overexpressed by malignant tissues, particularly by prostate cancer cells, including metastatic disease. Fluorine (^{18}F) is a β+ emitting radionuclide that enables positron emission tomography. Piflufolastat (^{18}F) is a selective secondgeneration fluorine-18-labeled small-molecule PSMA inhibitor. Based on the intensity of the signals, PET images obtained using piflufolastat (^{18}F) indicate the presence of PSMA expressing tissues.

Half-life

The biological or effective half-life of piflufolastate (^{18}F) is 3,47 ± 0,49 hours or approximately 70 minutes.

Pharmacodynamics

At the chemical concentrations used for diagnostic examinations, this medicinal product does not appear to have any pharmacodynamic activity.

Clinical efficacy

The safety and efficacy of Pylclari were evaluated in three prospective, open-label, multicenter clinical studies in men with prostate cancer: OSPREY (NCT02981368), CONDOR (NCT03739684), and PYTHON (EudraCT number 2020-000121-37).

OSPREY cohort A enrolled a cohort of 268 men with high-risk biopsy-proven prostate cancer (based on Gleason score, PSA score, and tumour stage) who were considered candidates for radical prostatectomy and pelvic lymph node dissection. Each patient received a single Pylclari PET/CT from mid-thigh to skull vertex. Three central independent readers blinded to all clinical information interpreted each PET scan for the presence of abnormal PSMA uptake in pelvic lymph nodes in multiple subregions, including the common iliac lymph nodes. Coprimary endpoints were specificity and sensitivity of Pylclari PET/CT compared to histopathology in the assessment of pelvic lymph nodes.

A total of 252 patients (94 %) underwent prostatectomy and pelvic lymph node dissection and had sufficient histopathology data for evaluation of the pelvic lymph nodes. Surgical specimens were separated into three regions: left hemipelvis, right hemipelvis, and other. For each patient, Pylclari PET/CT results and histopathology results obtained from redissected pelvic lymph nodes were compared by surgical region. PET/CT results in locations that were not redissected were excluded from analysis. For the 252 evaluable patients, the mean age was 64 years (range 46 to 84 years). The median serum PSA was 9,3 ng/mL. The total Gleason score was 7 for 19 %, 8 for 46 %, and 9 for 34 % of the patients, with the remainder of the patients having Gleason scores of 6 or 10.

The pre-defined thresholds for the co-primary endpoints were 40 % for sensitivity and 80 % for specificity. Sensitivity did not reach statistical significance for at least 2 of the 3 independent imaging reviewers, therefore, the endpoint was not reached.

Table 2 shows Pylclari PET/CT performance by reader using pelvic lymph node histopathology as reference standard of truth, at the patient level with region matching (one true positive region defines a true positive patient). Approximately 24% of the evaluable patients had pelvic lymph node metastases based on histopathology (95% confidence interval: 19 %, 29 %).

Table 2: Performance evaluation of Pylclari PET/CT for pelvic lymph node metastasis detection in OSPREY cohort A (n=252) using Patient-Level and Region-Matched analysis.

	Reader 1	Reader 2	Reader 3
True positive	23	17	23
False positive	7	4	9
False negative	36	43	37
True negative	186	188	183

Sensitivity, % (95-%-CI)	39 (27;51)	28 (17;40)	38 (26;51)
Specificity, % (95-%-CI)	96 (94;99)	98 (95;99)	95 (92;98)
PPV, % (95-%-CI)	77 (62;92)	81 (59;93)	72 (56;87)
NPV, % (95-%-CI)	84 (79;89)	81 (76;86)	83 (78;88)

Abbreviations: CI = confidence interval, PPV = positive predictive value, NPV = negative predictive value

For primary staging (OSPREY Cohort A), high level reader agreement for pelvic lymph nodes metastases (92,5 %) was achieved with Fleiss' kappa statistic of 0,78 (95 % CI: 0,71; 0.85).

In exploratory analyses, there were numerical trends towards more true positive results among patients with total Gleason score of 8 or higher and among patients with tumor stage of T2c or higher relative to those patients with lower Gleason score or tumor stage.

CONDOR included 208 patients with biochemical recurrence after initial treatment (radical prostatectomy in 85% of patients). The median serum PSA level was 0,82 ng/ml. All enrolled patients had conventional imaging (mostly CT or MRI) within 60 days prior to administration of Pylclari with negative or unclear findings. All patients received a PET/CT scan from the mid-thigh to the vertex with optional image acquisition of the lower extremities. Three independent central readers, blinded to all clinical information evaluated each PET/CT scan for the presence and location of positive lesions. The location of each lesion was divided into 5 regions (prostate/prostate bed, pelvic lymph nodes, other lymph nodes, soft tissue, bone). The primary endpoint was the correct localisation rate (CLR) at the patient level, defined as the percentage of patients who had at least one matching lesion on both Pylclari PET/CT imaging and the combined reference standard. If the lower bound of the 95% CI was > 0,2 for at least 2 of the 3 independent readers (20% CLR), the primary endpoint analysis was considered successful.

Depending on reader, a total of 123 to 137 patients (59% to 66%) had at least one lesion identified as positive for piflufolastate (^{18}F) PET (Table 3). PET-positive findings were most commonly observed in pelvic lymph nodes (40% to 42% of all PET-positive regions) and the least common region was soft tissue (6% to 7%).

Depending on reader, 99 to 104 patients with a piflufolastate (^{18}F)-PET-positive region had localisation-related information regarding the combined reference standard consisting of histopathology, imaging (CT, MRI, ultrasound, fluciclovine (^{18}F)-PET, choline PET or bone scan) within 60 days of the PET/CT scan, or PSA serum level response to targeted radiotherapy. Table 3 shows the patient-level results of the reader for PET/CT with Pylclari, including CLR.

Table 3. Patient-Level Performance of piflufolastat (^{18}F) PET/CT in CONDOR (n=208).

	Reader 1	**Reader 2**	**Reader 3**

PET-negative	71	84	85
PET-positive	137	124	123
True positive	89	87	84
False positive	15	13	15
Unevaluable (PET-positive without Reference Standard)	33	24	24
CLR % (95-% CI)	86 (79,92)	87 (80,94)	85 (78,92)

Abbreviations: CLR = location-matched positive predictive value, CI = confidence interval

Table 4 shows patient-level Pylclari PET/CT results from the majority read stratified by serum PSA level. Percent PET positivity was calculated as the proportion of patients with a positive PET/CT out of all patients scanned. The likelihood of a patient having at least one piflufolastat (^{18}F) PET-positive lesion generally increased with higher serum PSA level.

Table 4: Patient-Level Pylclari PET results and percent PET positivity* stratified by serum PSA level in the CONDOR study using majority result among three readers (n=199)**

PSA (ng/ml)	**PET-positive patients**				**PET-negative patients**	**Percent PET-positivity (95-% CI)***
	Total	TP	FP	Unevaluable (without reference standard)		
< 0,5	24	11	4	9	45	35 (24;46)
≥ 0,5 and < 1	18	12	3	3	18	50 (34;66)
≥ 1 and < 2	21	15	3	3	10	68 (51;84)
≥ 2	57	50	3	4	6	90 (83;98)
Total	120	88	13	19	79	60 (54;67)

* Percent PET positivity = PET positive patients/total patients scanned. PET positive patients include true positive and false positive patients as well as those who did not have reference standard information.
** Six patients were excluded from this table due to lack of baseline PSA level, and three patients were excluded from this table due to lack of majority result among three readers.
Abbreviations: TP = true positive, FP = false positive, CI = confidence interval

PYTHON was a randomised, open-label, cross-over study comparing piflufolastate (^{18}F) PET/CT and fluorocholine (^{18}F) PET/CT. It included 217 male patients with initial biochemical relapse after definitive therapy (radical prostatectomy (RP) ± prolonged lymph node dissection (eLND) in 73,2% of patients, percutaneous radiotherapyT or brachytherapy in 26,8% of patients). The primary endpoint was detection rate (DR) defined as the number of patients defined as positive at the patient level by independent readers, based on the total number of patients assessed (for piflufolastate (^{18}F) PET/CT and fluorocholine (^{18}F) PET/CT). A significant difference of 12 % detection rate in favour of piflufolastat (^{18}F) against Fluorocholine (^{18}F) was predefined.

201 patients performed one piflufolastat (^{18}F) PET/CT and one fluorocholine (^{18}F) PET/CT from mid-thigh to skull vertex in a randomised order. Three independent central readers, blinded to all clinical information, evaluated each piflufolastat (^{18}F) and each fluorocholine (^{18}F) PET/CT for the presence and location of positive lesions. Location of each lesion was categorized into 5 regions (prostate/prostate bed, pelvic lymph nodes, other lymph nodes, bone, soft tissue). Recurrence was detected by the blind read experts in 119 (60,4%) and 82 (41,0%) of the patients with piflufolastat (^{18}F) and fluorocholine (^{18}F) PET/CT, respectively. Details of overall independent reader's interpretation by PSA level is given in Table 5.

Table 5: Per-patient detection rate of PET/CT by PSA level in PYTHON study (N=201).

PSA (ng/mL) level at first injection	**piflufolastat (^{18}F)**	**fluorocholin (^{18}F)**
PSA < 0,2 (n=6)	2 (33,3 %)	1 (16,7 %)
PSA [0,2 - 0,5] (N=68)	24 (35,3 %)	21 (30,9 %)
PSA [0,51 - 1] (N=31)	17 (54,8 %)	10 (32,3 %)
PSA [1,01 - 2] (N=19)	13 (68,4 %)	6 (31,6 %)
PSA >2 (N=57)	50 (87,7 %)	39 (68,4 %)

Pharmacokinetics

Absorption

Pylclari is given intravenously.

Distribution

Blood levels drop biphasic. The distribution half-life is 0,17 ± 0,04 hours and the elimination half-life is 3,47 ± 0,49 hours.

Physiological accumulation of piflufolastate (^{18}F) is observed in the kidneys (16,5% of administered activity), liver (9,3%) and lungs (2,9%) within 60 minutes of intravenous administration. Most of the remaining 70% of the activity in 60 minutes is with the rest of the body-background region.

Metabolism

No data available.

Elimination

The only radioactive component detected in plasma samples by high-performance liquid chromatography (HPLC) up to 173 minutes post-injection was unchanged piflufolastat (^{18}F). Elimination

is by urinary excretion. In the first 8 hours post-injection, approximately 50% of administered radioactivity is excreted in the urine.

Kinetics in specific patient groups

Renal/hepatic impairment

Pharmacokinetics have not been described in patients with renal or hepatic impairment.

Preclinical data

In rats, an extended single dose study of toxicity was conducted with the non-radioactive medicinal product. No adverse effects were observed up to the maximum dose of 0,5 mg/kg. This dose is more than 875-fold higher than the maximum clinical dose of 40 µg/patient (or 0,5714 µg/kg for a reference body weight of 70 kg).

No further studies on mutagenic or carcinogenic potential and reproductive toxicity have been performed.

Other information

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section titled “Instructions for handling”.

Effects on diagnostic methods

Keine Daten vorhanden.

Shelf life

Der Verfallszeitpunkt ist 11 Stunden nach Markierung.
Tag und Zeitpunkt des Ablaufs sind auf den Etiketten angegeben.

Nach dem Verdünnen maximal 4 Stunden lagern, ohne den Verfallszeitpunkt zu überschreiten.

Special precautions for storage

Store in the original lead shielding.
Do not store above 30°C. Chemical and physical stability has been demonstrated for 11 hours at 40°C.

For storage conditions after first removal of the medicinal product, see section “Shelf life”.

Storage of radiopharmaceuticals must be in accordance with national regulations on radioactive substances.

Instructions for 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 licences 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.

Precautions before/during handling or administration of the medicinal product
Before use, the packaging should be checked and the activity of the solution measured with an activity meter. If at any time the integrity of the vial is compromised, do not use it. The solution should be visually inspected prior to use. Only clear solutions that are free from visible particles should be used.
Use should be carried out in such a way as to minimise the risk of contamination of the medicinal product and radiation exposure of the operators. Adequate shielding is absolutely necessary.

This ready-to-use medicine can be diluted with sodium chloride 9 mg/ml (0,9%) solution for injection.

The appropriate volume should be removed under aseptic conditions. Do not open the vial. After disinfection of the stopper, the solution should be drawn up over the stopper with a single-dose syringe fitted with an appropriate protective shield and a sterile disposable needle, or with an approved automated and qualified delivery system.

This product is administered via an intravenous flexible catheter. The administration must be strictly intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artefacts. The bolus administration will be followed by a flush of 5-10 mL sodium chloride 9 mg/mL (0.9 %) solution for injection, to ensure full delivery of the dose.

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

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

This medicinal product should only be used when the injection volume is greater than 0,2 mL. If the injection volume is between 0,2 and 1 mL, only syringes of an appropriate size (1 mL) should be used.

Authorisation number

69775

Packs

15 ml colourless type I glass vial closed with a chlorobutyl stopper and aluminium seal.

Pack size: One multidose vial contains 0,5 ml to 10 ml of solution equivalent to:

- 500 to 10 000 MBq at the time of calibration of Pylclari 1 000 MBq/ml [A]
- 750 to 15 000 MBq at the time of calibration of Pylclari 1 500 MBq/ml [A]

Marketing authorisation holder

b.e. imaging AG, 6340 Schwyz

Date of revision of the text

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