SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Pylclari 1 000 MBq/mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

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.

Excipient(s) with known effect

Each ml of solution contains a maximum of 3.5 mg of sodium and 90 mg of ethanol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution with a pH ranging from 4.5 to 7.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of 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 (^{18}F) piflufolastat 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

Piflufolastat (^{18}F) 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.

Piflufolastat (^{18}F) has not been studied in patients with hepatic impairment.

Paediatric population

There is no relevant use of piflufolastat (^{18}F) in the paediatric population.

Method of administration

It is administered by a single intravenous injection.

Pylclari is presented in multidose vial. The minimal volume is 0.5 ml of solution per vial.

The volume of solution to be administered can range from 0.2 ml to 10 ml.

Precautions to be taken before handling or administering the medicinal product

For instruction before administration, see section 6.6.

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

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.

For patient preparation, see section 4.4.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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.

Renal impairment

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

Paediatric population

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

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 act within the uptake time period may be administered to improve interpretation of piflufolastat (^{18}F) PET/CT as it results in less activity depositions in ureters and the bladder.

After the procedure

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

Interpretation of piflufolastat (^{18}F) images

The recommended method for PET images interpretation with piflufolastat (^{18}F) 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.

Piflufolastat (^{18}F) 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 (Paget's disease), pulmonary sarcoidosis/granulomatosis).

Images should be interpreted only by readers trained in the interpretation of PET images with piflufolastat (^{18}F).

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.

Piflufolastat (^{18}F) was not studied for detection of distant metastases in primary staging.

The performance of piflufolastat (^{18}F) for imaging of patients with biochemical evidence of recurrence of prostate cancer seems to be affected by serum PSA levels (see section 5.1). The performance of piflufolastat (^{18}F) 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 piflufolastat (^{18}F) 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 piflufolastat (^{18}F) PET/CT findings only.

Specific warnings

This medicinal product contains up to 3.5 mg sodium per ml equivalent to 0.2 % to the WHO recommended maximum daily intake of 2 g sodium 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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Androgen deprivation therapy (ADT) and other therapies targeting the androgen pathway, such as androgen receptor antagonists, may result in changes in uptake of piflufolastat (^{18}F) in prostate cancer. The effect of these therapies on performance of piflufolastat (^{18}F) PET has not been established.

Chronic treatment with diuretics does not seem to have any interference with piflufolastat (^{18}F) for interpretation of images.

4.6 Fertility, pregnancy and lactation

Pregnancy

Piflufolastat (^{18}F) is not intended for use in women.

Breast-feeding

Piflufolastat (^{18}F) is not intended for use in women.

Fertility

No studies on fertility have been performed.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

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. 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 (³1/1 000 to <1/100), Rare (³1/10 000 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 piflufolastat (^{18}F)

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.

Description of selected adverse reactions

A total of 108 treatment emergent adverse events (TEAEs) were reported in 69 (8.6 %) patients, with headache (1.4%), dysgeusia (1.0%), and fatigue (0.5%) being the most frequent. Three serious drug-related adverse events (hypersensitivity, headache, and paresthesia) were reported, all experienced by one patient and only hypersensitivity was assessed as drug-related in this patient who had a significant history of allergic reactions. All three serious drug-related adverse events were resolved.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects.

As the effective dose is 4.4 mSv when the maximal recommended activity of 360 MBq is administered in a 70 kg-weighted patient, these adverse reactions are expected to occur with a low probability.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The maximum amount of piflufolastat (^{18}F) 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals, other diagnostic radiopharmaceuticals for tumour detection, 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 second-generation 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.

Pharmacodynamic effects

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 piflufolastat (^{18}F) were evaluated in three prospective, open-label, multi-center 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 who were considered candidates for radical prostatectomy and pelvic lymph node dissection. Each patient received a single piflufolastat (^{18}F) 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 uptake in pelvic lymph nodes in multiple subregions, including the common iliac lymph nodes. Co-primary endpoints were specificity and sensitivity of piflufolastat (^{18}F) PET/CT against histopathology within the pelvic lymph nodes. Secondary endpoints were Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of piflufolastat (^{18}F) PET/CT to predict the presence or absence respectively of prostate cancer within the prostate gland and lymph nodes in Cohort A.

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, piflufolastat (^{18}F) PET/CT results and histopathology results obtained from dissected pelvic lymph nodes were compared by surgical region. PET/CT results in locations that were not dissected 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, it was considered a failed study.

Table 2 shows piflufolastat (^{18}F) PET/CT performance by Reader using pelvic lymph node histopathology as 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 piflufolastat (^{18}F) 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.

A comparison on diagnostic performance of piflufolastat (^{18}F) PET/CT with baseline conventional imaging (CI) in patients with high-risk prostate cancer from Osprey Cohort A was performed as a post-hoc study. Piflufolastat (^{18}F) PET/CT demonstrated a 3-fold higher PPV than conventional imaging (median 86.7% vs. 28.3%, respectively) despite similar sensitivity (median 40.3% for piflufolastat (^{18}F) PET/CT and 42.6% for conventional imaging). Mean specificity of piflufolastat (^{18}F) PET/CT was 97.9% and 65.1% for CI and mean NPV 83.2% vs. 78.8% respectively.

CONDOR enrolled 208 patients with biochemical evidence of suspected recurrent prostate cancer after initial treatment (radical prostatectomy in 85% of the patients). The median serum PSA was 0.82 ng/mL. All enrolled patients had negative or equivocal for prostate cancer conventional imaging evaluation (for most patients, CT or MRI) within 60 days prior to receiving piflufolastat (^{18}F). All patients received a single PET/CT from mid-thigh to skull vertex with optional imaging 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. Location of each lesion was categorized 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 for whom there was a one-to-one correspondence between localisation of at least one lesion identified on piflufolastat (^{18}F) PET/CT imaging and the composite truth standard. If the lower bound of the 95% CI was >0.2 (CLR of 20%) for at least 2 of the 3 independent imaging reviewers, then the primary endpoint analysis was considered a success. The secondary endpoint was the impact on patient management (IMP) defined as the percentage of patients with a change in intended prostate cancer treatment plans due to piflufolastat (^{18}F) PET/CT as measured by comparison of intended management questionnaires completed pre- and post- piflufolastat (^{18}F) PET/CT imaging results.

Depending on the reader, a total of 123 to 137 patients (59% to 66%) had at least one lesion that was identified as piflufolastat (^{18}F) PET-positive (Table 3). The region most commonly observed to have a PET-positive finding was pelvic lymph nodes

(40% to 42% of all PET-positive regions) and the least common region was soft tissue (6% to 7%).

Depending on the reader, 99 to 104 patients with a piflufolastat (^{18}F) PET-positive region had location-matched composite reference standard information that consisted of histopathology, imaging (CT, MRI, ultrasound, fluciclovine (^{18}F) PET, choline PET, or bone scan) obtained within 60 days of the PET/CT scan, or response of serum PSA level to targeted radiotherapy. Table 3 shows patient-level performance results of piflufolastat (^{18}F) PET/CT by reader, including location-matched positive predictive value, also known as Correct Localization Rate (CLR). A patient was considered true positive if they had at least one matching location positive on both piflufolastat (^{18}F) PET/CT and the composite reference standard.

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 piflufolastat (^{18}F) 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 piflufolastat (^{18}F) 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

For the 207 patients with medical management questionnaires completed by treating physicians at pre-and post-PSMA imaging, 64% (131/207) of patients had a change in intended management after piflufolastat (^{18}F) PET/CT. Of the patients with changed clinical plans, 79% (103/131) were due to positive PSMA PET/CT findings, and 21% (28/131) were due to negative scans. The most frequent changes were from salvage local therapy to systemic therapy (58 patients), from observation to initiating any therapy (49 patients), from noncurative systemic therapy to salvage local therapy (43 patients), and from planned treatment to observation (no treatment) (9 patients).

PYTHON was a randomised, open-label, two-treatment cross-over study. It enrolled 217 male patients with first biochemical recurrence of prostate cancer, who underwent definitive therapy (radical prostatectomy (RP) ± extented lymph node dissection (eLND) in 73.2% patients, EBRT or brachytherapy in 26.8% patients). The primary endpoint was detection rate (DR) defined as number of patients defined as positive at patient level by the independent readers among the total number of patients assessed (for piflufolastat (^{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 pre-defined. Secondary endpoints were sensitivity (ratio between the number of patients defined as positive for a given region by the independent readers and the total number of patients assessed as positive for a given region by the truth panel), concordance (ratio between the number of regions defined as positive by both piflufolastat (^{18}F) PET/CT and Fluorocholine (^{18}F) PET/CT + the number of regions defined as negative by both piflufolastat (^{18}F) PET/CT and Fluorocholine (^{18}F) PET/CT and the total number of assessed regions) and impact on patient management.

Two-hundred one 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)**	**fluorocholine (^{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%)

Per-patient sensitivity was assessed for 37 patients with a standard of truth and is reported in Table 6. Per-patient sensitivity of (^{18}F)-piflufolastat was significantly higher than that of (^{18}F)-fluorocholine ($p<0.0001$).

Table 6: Per-patient sensitivity (n=37)

PET/CT	**piflufolastat (^{18}F)**	**fluorocholine (^{18}F)**
Sensitivity (95% CI)	58.3% (95% CI 51.5;64.9)	40.6% (95% CI 34.1;47.5)

The concordance rate between ^{18}F-piflufolastat PET/CT and ^{18}F-fluorocholine PET/CT according to central blind readers, per-region was remarkably high for all regions of interest, namely prostate bed :87.3% (81.9; 91.3), pelvic lymph nodes: 73.9% (67.3; 79.5), extrapelvic lymph nodes: 86.5% (81.0; 90.6), bones: 86.9% (81.5;91.0), and other organs: 92.0% (87.3; 95.1).

Regarding the localization of recurrence, the central readers achieved an agreement of 84.2% with a Fleiss' kappa statistic of 0.58 (95% CI: 0.47; 0.70) for all biopsy images in OSPREY Cohort B. In CONDOR, the central readers exhibited 76% agreement in interpreting positive or negative piflufolastat (18F) PET/CT scans with a Fleiss' kappa statistic of 0.65 (95% CI: 0.58; 0.73), while the concordance between each central Reader and the local Reader ranged from 83% to 84%. In PYTHON, the inter-Reader agreement percentage was 67.8%, and the corresponding Fleiss' kappa was 0.55 (95% CI: 0.47; 0.63).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Pylclari in all subsets of the paediatric population in diagnosis of prostate cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Distribution

Blood levels decline in a biphasic fashion. The distribution half-life is 0.17 ± 0.04 hours and the elimination half-life is 3.47 ± 0.49 hours.

Organ uptake

Physiologic accumulation of piflufolastat (^{18}F) is observed in the kidneys (16.5% of administered activity), liver (9.3%), and lung (2.9%), within 60 minutes of intravenous administration. Most of the remaining 70% of activity at 60 minutes is with the rest of the body background region.

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.

Half-life

The biological and effective half-life of piflufolastat (^{18}F) are 3.47 ± 0.49 hours and approximately 70 minutes, respectively.

Renal/Hepatic impairment

The pharmacokinetics in patients with renal or hepatic impairment have not been characterised

5.3 Preclinical safety data

An extended single dose toxicity study was conducted in rats with the non-radioactive pharmaceutical. No adverse reactions were observed in any of the animals, and no deaths occurred at the highest tested dose of 0.5 mg/kg. This dose is over 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); on a body surface area basis, this dose is approximately 142-fold higher, suggesting adequate safety margin.

No other studies were conducted.

This medicinal product is not intended for regular or continuous administration. At the chemical concentrations and the activities used for diagnostic examinations, additional studies does not appear to be necessary.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol

Sodium chloride 9 mg/mL (0.9%) solution for injection

Sodium ascorbate

6.2 Incompatibilities

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

6.3 Shelf life

11 hours from the end of manufacturing.

Date and time of expiry are indicated on the labels.

After the first withdrawal, this medicinal product does not require any special storage conditions.

After dilution, store for up to 4 hours without exceeding the expiry time.

6.4 Special precautions for storage

Store in the original lead shielding.

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

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

6.5 Nature and contents of container

15 ml colourless Type I glass vial, closed with a chlorobutyl stopper and an aluminium seal.

Pack size: one multidose vial contains 0.5 ml to 10 ml of solution, corresponding to:

- 500 to 10 000 MBq at calibration time of Pylclari 1 000 MBq/mL

6.6 Special precautions for disposal

General warning

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate 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 to be taken before handling or administering the medicinal product

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.

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

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

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

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

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

7 MARKETING AUTHORISATION HOLDER

Curium Pharma UK Ltd
Suite 211b Central
Second Floor, Building 1000
Lakeside North Harbour
Portsmouth
PO6 3EN
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 44301/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/03/2024

10 DATE OF REVISION OF THE TEXT

03/09/2025

11 DOSIMETRY

Data listed below are from sponsored clinical studies.

Assumptions:

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.

Piflufolastat (^{18}F) exhibits bi-exponential behaviour in blood, with a distribution half-life of 0.17 ± 0.044 hours and an elimination half-life of 3.47 ± 0.49 hours. It distributes to the kidneys (16.5% of administered activity), liver (9.3%), and lung (2.9%), within 60 minutes of intravenous administration.

Methodology:

The time-integrated activity in source tissue was obtained from longitudinal imaging data. Contours or volumes of interest (VOIs) were typically drawn around different activity-containing organs that were identified on each image at each time-point. The S-value was obtained by Monte Carlo simulation. The absorbed doses calculation was performed on 3D-RD-S software. The resulting effective dose was calculated according to ICRP 103.

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	
Stomach wall	0.0127
Small Intestine wall	0.0101
Colon Wall	
Upper large intestine wall	0.0125
Lower Large Intestine wall	0.0101
Heart wall	0.0178
Kidneys	0.124
Liver	0.0388
Lungs	0.0121
Muscles	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, 13.4 mgy and 10.2 mgy respectively.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Method of preparation

This ready-to-use medicinal product can be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection.

Withdrawals of the appropriate volume should be performed under aseptic conditions. The vial must not be opened. After disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated and qualified application system.

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

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.

Quality control

The packaging must be checked before use and the activity of the solution must be measured using an activimeter.

The solution should be inspected visually prior to use. Only clear solution, free of visible particles should be used.