PYLARIFY NCCN Submission Request

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To: NCCN Guidelines Prostate Cancer Panel

On behalf of Lantheus Holdings, Inc., we respectfully request the Panel to review the enclosed data supporting the use of PYLARIFY® (piflufolastat F 18) injection ("piflufolastat F 18") (previously referred to as ^{18}F-DCFPyL) as a radioactive diagnostic agent in positron emission tomography (PET) of prostate-specific membrane antigen (PSMA)-positive lesions in men with prostate cancer with 1) suspected metastasis who are candidates for initial definitive therapy, or 2) suspected recurrence based on elevated serum prostate-specific antigen (PSA) level.

***Approval status*:** On 5/26/21, the US Food and Drug Administration (FDA) approved piflufolastat F 18 for these indications.[1]

***Specific changes sought*:** added text is shown in **bold**, deletions in "~~strikethrough~~", and the text location in *italicized, underlined type*; page numbers refer to *NCCN Guidelines Version 2.2021 Prostate Cancer.*

"Initial risk stratification and staging work-up for clinically localized disease" Table (PROS-2; p 10 of 178)
"Unfavorable intermediate" risk group cell, "High" risk group cell, and "Very high" risk group cell in "Imaging" column:
Whole-body imaging with piflufolastat F 18 PET/CT: **recommended**

Footnote to "Initial risk stratification and staging work-up for clinically localized disease" section (PROS-2A; pg 11 of 178)
Footnote h: …MRI, **piflufolastat F 18 PET/CT,** F-18 sodium…can be considered for equivocal results on initial bone scan…

Footnote to the following sections: "Monitoring" (PROS-10; pg 20 of 178), "Radical prostatectomy PSA persistence/recurrence" (PROS-11; pg 21 of 178), "Radiation therapy recurrence" (PROS-12; pg 22 or 178; and PROS12-A; pg 23 of 178), "Systemic therapy for castration-naïve prostate cancer" (PROS-13; pg 24 of 178), "Systemic therapy for M0 castration-resistant prostate cancer (CRPC)" (PROS-14; pg 25 of 178)
Footnote hh: …consider **piflufolastat F 18 PET/CT,** C-11 choline…for further soft tissue and bone evaluation…

"Radical prostatectomy PSA persistence/recurrence" section (PROS-11; pg 21 of 178)
"PSA persistence/recurrence" portion of algorithm (2nd bullet from bottom, 2nd column to left): **Piflufolastat F 18 PET/CT, or** C-11 choline or F-18 fluciclovine PET/CT or PET/MRI[f,w,ll]

Footnote to: "Radical prostatectomy PSA persistence/recurrence" section (PROS-11; pg 21 of 178), "Radiation therapy recurrence" section (PROS12-A; pg 23 of 178)
Footnote kk: **Piflufolastat F 18 PET/CT** or F-18 sodium fluoride**,** or C-11 choline**,** or F-18 fluciclovine PET/CT or PET/MRI can be considered after bone scan for further evaluation…

"Radiation therapy recurrence" section (PROS-12; pg 22 of 178)
"PSA persistence/recurrence or Postive DRE" portion of algorithm (bottom bullet, second column to left) (PROS-12, pg 22 of 178): **Piflufolastat F 18 PET/CT or** C-11 choline or F-18 fluciclovine PET…

"Principles of imaging" section (PROS-C; pp 32–34 of 178)
"Bone Imaging" section, pg 2 of 3 of PROS-C (pg 33 of 178): Plain films, CT, MRI, **piflufolastat F 18 PET/CT,** F-18 sodium fluoride PET/CT or PET/MRI, C-11 choline PET/CT…can be considered for equivocal results on initial bone scan.

"Positron Emission Tomography (PET)" section, pg 3 of PROS-C, left column (pg 34 of 178):
Piflufolastat F 18 PET/CT or C-11 choline…may be used to detect small-volume disease in soft tissues and in bone.

Discussion (MS-10–MS-67, pp 63–120 of 178) [Note: citations in bold refer to list at end of this Submission Request]
"Initial clinical assessment and staging evaluation" section (MS-10, pg 63 of 178)
Conventional bone scan is recommended first, with subsequent…MRI, or **piflufolastat F 18 PET/CT,** F-18 sodium fluoride…
"Nuclear Imaging" section (MS-11–MS-12, pp 64–65 of 178)
First paragraph of section: ~~Three~~ **Five** PET tracers are FDA cleared…**piflufolastat F 18, Ga-68 PSMA-11,** C-11 choline...
Second paragraph of section: "**Piflufolastat F 18 PET/CT,** C-11 choline…or PET/MRI detect small-volume disease in bone and soft tissues.[178,179,2,3] **The sensitivity point estimates of piflufolastat F 18 PET/CT in detecting pelvic nodal involvement in newly-diagnosed patients in two prospective studies with samples totaling >100 patients with unfavorable intermediate-risk, high-risk, or very high-risk prostate cancer range from 40.3%[3] to 41.2%,[4] while the specificity point estimates range from 94.0%[4] to 97.9%.[3] In the primary staging setting, piflufolastat F 18 PET/CT findings led to re-classification of 27% of patients and to changes in treatment recommendations in 39% in a prospective study,[5] while the modality detected evidence of metastatic disease not seen on CT in 17% of patients in a retrospective analysis.[6] In men with biochemical recurrence, the reported correct localization rate of piflufolastat F 18 PET/CT (patient-level positive predictive value + anatomic co-localization) range from 84.8% to 87.0%.[2] The reported patient-level lesion detection rate for piflufolastat F 18 ranges from 50% to 60% in men with PSA <0.5 ng/mL and from 69% to 78% in those with PSA ≥0.5–<1.0 ng/mL,[7-9] and was 59% in men with PSA <1.0 ng/mL in another study.**[10] The reported sensitivity and specificity of C-11 choline…and agreement was 85%.[186] **In men with biochemical recurrence after definitive therapy, piflufolastat F 18 PET/CT findings changed intended management for 63.9% of evaluable patients in the CONDOR study,[2] and PET/CT findings led to actual major management changes in 59% of patients in another prospective multicenter study.**[11] The FALCON…The panel believes that **piflufolastat F 18 PET/CT,** F-18 fluciclovine…may be used… for further soft tissue and/or bone evaluation…
Fourth paragraph of section:
The panel believes that **piflufolastat F 18 PET or** F-18 sodium fluoride…may be considered after bone scan for further evaluation of the bones when bone scan results are equivocal.
"Disease Monitoring", "Workup for Progression" subsection (MS-33, pg 86 of 178):
Piflufolastat F 18 PET/CT or C-11 choline…can be considered for further soft tissue and bone evaluation…
"*Biochemical Recurrence after Radical Prostatectomy" (MS-36, pg 89 of 178):*
…**piflufolastat F 18 PET/CT,** C-11 choline PET/CT or PET/MRI**,**…prostate bed biopsy may be useful.
"*Post-Irradiation Recurrence" section (MS-37, pg 90 of 178):*
…in addition, a chest CT…MRI; **piflufolastat F 18 PET/CT or** C-11 choline PET/CT or PET/MRI…can be considered.

Tracer	Half-life (min)	Cyclotron	Mechanism of action	Excretion	Sensitivity (%)	Specificity (%)*	FDA Status	Panel Recommendations
Piflufolastat F 18	**110**	**Regional**	**PSMA analog**	**Renal**	**40.3%–41.2% point estimates to detect nodal involvement in primary staging of unfavorable intermediate-risk, high-risk, and very high-risk patients** **84.8%–87.0% correct**	**94.0%–97.9% point estimates to detect nodal involvement in primary staging of unfavorable intermediate-risk, high-risk, and very high-risk patients** **Specificity in biochemical**	**Cleared**	**May be used to detect metastases in newly-diagnosed unfavorable intermediate-risk patients with clinically-localized disease if nomogram predicts >2% probability of pelvic lymph node involvement** **May be used to detect metastases in high-risk**

					localization rate (patient-level positive predictive value + anatomic lesion co-localization)	**recurrence setting not reported**		**and very high-risk newly-diagnosed patients with clinically-localized disease** **May be used to detect biochemically-recurrent small-volume disease in soft tissues** **May be used after bone scan to further evaluate equivocal findings**

Table 2 (MS-66, pg 119 of 178): **New row immediately beneath the column headers row:**

Rationale for piflufolastat F 18 PET/CT use prior to initial definitive therapy*:* Results of the prospective, multi-center, phase 2/3 OSPREY study[3] support the utility of piflufolastat F 18 PET/CT in the evaluation of men with suspicion of metastases. OSPREY included 252 evaluable patients with high-risk or very high-risk disease (clinical stage ≥T3a or PSA >20 ng/mL or Gleason score ≥8) who underwent radical prostatectomy (RP) with pelvic lymph node dissection (PLND). Histopathology was the standard of truth. Piflufolastat F 18 PET/CT attained OSPREY's specificity co-primary endpoint: median (95% confidence interval [CI]) patient-level specificity for pelvic nodal involvement was 97.9% [94.5%–99.4%]) among the study's 3 readers, and the lower limit of that 95% CI for all readers (93.6%–96.0%) amply exceeded the prespecified 80% threshold. Further, piflufolastat F 18 PET/CT achieved high positive predictive value (PPV) (78.1%–90.5%, lower limits of 95% CIs, 63.8%–69.9%), reflecting strong likelihood that piflufolastat F 18-positive lesions indeed represented prostate cancer. Piflufolastat F 18 PET/CT had a median sensitivity (95% CI) of 40.3% (28.1%–52.5%); since the lower limit of that CI did not exceed the 40% prespecified threshold, the study's sensitivity co-primary endpoint was not met. However, in a post hoc analysis excluding patients with micrometastatic disease whose largest lesion was ≤5 mm (n = 27/252, 10.7%), the median (95% CI) sensitivity was 60% (44%–76%). The post hoc analysis was performed to address the discrepancy between the abilities of histopathology and PET to identify microscopic lesions, consistent with limitations in spatial resolution of all PET scanners.[12] A further notable OSPREY finding was a 12.3% patient-level extrapelvic lesion detection rate (33/268 patients evaluable for this variable) based on findings from ≥1 reader, potentially aiding decision-making regarding systemic treatment. In the SALT prospective multicenter study[4] (n = 117 evaluable), which also used histopathology as the standard of truth, and included intermediate-risk as well as high-risk and very-high-risk patients, piflufolastat F 18 PET/CT had specificity and PPV to detect nodal metastases (94.0% [95% CI 86.9%–97.5%] and 90.4% [95% CI 82.6%–95.0%], respectively) comparable to those in OSPREY. Piflufolastat F 18 PET/CT sensitivity (95% CI) to detect nodal metastases was 41.2% (19.4%–66.5%) in the SALT study[4] and 71.4% (29%–96.3%) in a single-center Phase II trial[13] (n = 25 evaluable). Notably, piflufolastat F 18 PET/CT detected nodal metastases not seen on CT in 17% of patients in a 160-patient retrospective analysis,[6] and changed pre-specified treatment recommendations in 39% of men in a 100-patient prospective study[5] which included unfavorable intermediate-risk, high-risk, and very high-risk patients.

Specific rationale for piflufolastat F 18 PET/CT use in the biochemical recurrence (BCR) setting: Results of the prospective, multicenter, phase 3 CONDOR study[2] support piflufolastat F 18 PET/CT use in the BCR setting. This study supports the modality's strong diagnostic performance overall, for both nodal and distant metastases, and in patients with low PSA levels, as well as impact on staging and disease management planning. CONDOR included 208 men with rising PSA ≥0.2 ng/mL after RP or ≥2 ng/mL above nadir after radiation therapy (RT). Of the study sample, 49.5% had RP only, 35.6%, RP + RT, and 14.9%, RT only. Median (minimum–maximum) PSA was 0.8 (0.17–98.45) ng/mL (n = 202); 68.8% of patients (139/202) had PSA <2 ng/mL. The CONDOR study enrolled patients who had negative or equivocal conventional imaging. In agreement with the FDA, CONDOR's primary endpoint, correct localization rate (CLR), incorporated patient-level PPV plus anatomic lesion co-localization relying on a composite tiered standard of truth. That

standard of truth comprised, in descending priority and depending upon data availability: 1) histopathology, used in 23.5% of evaluable patients; 2) correlative imaging (used in 75.8%) with PET, focused MRI or CT; or 3) PSA response to subsequent RT, used in 1 case. Piflufolastat F 18 PET/CT achieved a high CLR of 84.8%–87.0% across three independent readers. Importantly, CLRs ranged from 33.3%–42.0% in patients with PSA <0.5 ng/mL (n = 69), from 45.9%–56.8% in men with PSA 0.5–<1.0 ng/mL (n = 37), and from 57.6%–72.7% in those with PSA 1–<2 ng/mL (n = 33). Additionally, piflufolastat F 18 PET/CT provided actionable information in the majority of cases: scan findings changed intended management, a secondary endpoint, in 63.9% of evaluable patients (131/205), based on pre- and post- piflufolastat F 18 physician questionnaires. Also in the BCR setting, piflufolastat F 18 PET/CT findings were associated with major management changes in 59% of cases based on chart review in an additional prospective study,[11] and with improved decision-making in 89.1% of cases in another questionnaire-based prospective study.[8]

Additional rationale supporting requested changes: The safety and tolerability profile of piflufolastat F 18 also supports our requested changes. As noted in FDA-approved product labeling, in 593 patients in OSPREY and CONDOR, each given a single i.v. injection of a mean 340 ± 26 MBq (9.2 ± 0.7 mCi) activity, the most common adverse reactions observed in >0.5% were headache and dysgeusia in 2% each, and fatigue in 1%; 1 patient, with a significant history of allergic reaction, experienced a delayed hypersensitivity reaction.[1-3]

We thank the NCCN Panel for their consideration of this Submission Request.

Sincerely,

Bela Denes, MD
Vice President, Global Medical Affairs

REFERENCES CITED AND ENCLOSED

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4. Jansen et al. Pelvic lymph-node staging with (18)F-DCFPyL PET/CT prior to extended pelvic lymph-node dissection in primary prostate cancer - the SALT trial. *Eur J Nucl Med Mol Imaging.* 2021;48(2):509-520.
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