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NCCN Guidelines Panel: Prostate Cancer

On behalf of Blue Earth Diagnostics Ltd., we respectfully request the NCCN Prostate Cancer Panel to review the enclosed data supporting the use of PET imaging with Axumin™ (fluciclovine F 18) in men with suspected prostate cancer recurrence based on elevated blood PSA levels following prior treatment.

Approval status: On May 27, 2016 the FDA approved Axumin™ (fluciclovine F 18) for the following indication: *PET imaging with fluciclovine F 18 in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment.*

Specific Change requested: We request addition of fluciclovine F 18 to the list of imaging techniques recommended for detection of prostate cancer recurrence in men with biochemical recurrence (BCR).

Rationale: Fluciclovine F 18 is a positron emitting imaging agent that was recently approved by FDA for imaging of prostate cancer in men with BCR.[1] The compound is a synthetic amino acid that is preferably taken up by amino acid transporters in tissues that need increased amounts of amino acids to support increased metabolism and proliferation. Imaging studies with histological confirmation have demonstrated that uptake of the fluciclovine F 18 is enhanced in prostate cancer in the prostate bed, involved lymph nodes and bony metastases. Thus, this biochemically relevant localization method may be useful to evaluate suspected nodal or metastatic disease where confirmation or exclusion of pelvic and/or distant disease would directly influence patient management.

Unfortunately, up to a third of patients treated with definitive local therapy for prostate cancer [PCa] will experience recurrent disease. [2,3] Management requires detection and appropriate treatment of local, regional and distant disease locations, but PSA rises suggestive of residual or recurrent disease are frequently accompanied by a failure to detect the disease location(s) using conventional imaging tools such as CT and bone scintigraphy [BS]. Both CT and BS are of limited utility until PSA values rise to 10-20 ng/ml. Kane et al reported that patients with BCR after radical prostatectomy have a low probability of a positive BS (9.4%) or a positive CT scan (14.0%) within 3 years of biochemical recurrence. [4] Similarly, in men with BCR at a median time of 5 years post-surgery, of the 380 bone scans done among hormone-naive subjects only 24 (6%) were positive and 356 (94%) were negative for metastasis.[5] CT images, although highly specific when positive, do not raise suspicion if the involved LN is <1 cm in diameter, even if the node is cancerous. ^{18}F FDG PET is of limited use in BCR[6] because uptake in PCa is generally suboptimal until the patient has metastatic castrate resistant disease, and physiologic excretion of FDG in the bladder may interfere with image interpretation of adjacent structures in the pelvis.

However, salvage radiation therapy (SRT) to the prostate should be initiated well before a PSA of 10 – 20 ng/mL is reached, as studies have demonstrated that outcomes are better if SRT is initiated at low (e.g. <0.5 ng/mL) PSA values[7 and refs therein] and is not curative if the disease has progressed to the point where it can be seen on bone scans.

Fluciclovine F 18, which uses positron emission tomography (PET) in conjunction with CT, is now approved for the detection of recurrent PCa. Studies comparing the agent to the gamma-emitting PSMA targeted agent ProstaScint, and to CT and ^{11}C-choline have been reported, as has its use in primary prostate cancer and in therapy planning. The results indicate that fluciclovine has significantly improved sensitivity relative to CT (the standard of care) and ProstaScint, and has higher sensitivity than 11C-choline at PSA values less than 1 ng/mL in

men with BCR. **We believe that this novel molecular imaging agent offers a unique and useful method to identify recurrent disease and request consideration of the following data.**

In an NIH funded prospective RO1 study at Emory University, 115 patients with BCR and negative ^{99m}Tc bone scans after radical prostatectomy or radiotherapy were imaged with fluciclovine F 18. The majority (n=93) also received ^{111}In capromab pendetide (ProstaScint) to compare the regional sensitivity and specificity of the two agents, relative to histology and clinical follow-up.[8] Sufficient data for truth assessment (histology, response to therapy and clinical follow-up) were available in 91 patients for prostate/bed findings and in 70 patients with extraprostatic involvement. The following results were found:

Agent	Location	Sensitivity	Specificity	Accuracy	PPV	NPV
Fluciclovine F 18 (n=91)	Prostate/ bed	90.2%	40.0%	73.6%	75.3%	66.7%
ProstaScint (n=91)		67.2%	56.7%	63.7%,	75.9%	45.9%
Fluciclovine F 18 (n=70)	Extraprostatic sites	55.0%	96.7%	72.9%	95.7%	61.7%
ProstaScint (n=70)		10.0%	86.7%	42.9%	50.0%	41.9%

Of the 77 index lesions used to prove positivity, histological proof of PCa was obtained in 74 (96.1%). Fluciclovine F-18 identified 14 more positive prostate bed recurrences (55 vs 41) and 18 more subjects with extraprostatic involvement (22 vs 4). The agent upstaged 25.7% of the patients. For fluciclovine, imaging was complete within 40 min post-injection (PI), in contrast to ^{111}In capromab pendetide where images were obtained at 3 days PI.

A secondary endpoint of the above study[9] analyzed a subset of this group (n=53) to compare the ability of CT and fluciclovine F 18 to detect recurrent disease. On a whole-body basis, 41/53 fluciclovine PET/CT scans (77.4%) were positive, but only 10/53 scans (18.9%) were positive with CT. Of 33 patients with histological proof of disease, fluciclovine PET/CT detected disease in 31 (93.9%) but CT detected disease in only 4 (12.1%). The authors concluded that the diagnostic performance of fluciclovine PET/CT in recurrent prostate cancer is superior to that of CT, and provides better delineation of prostatic from extraprostatic recurrence.

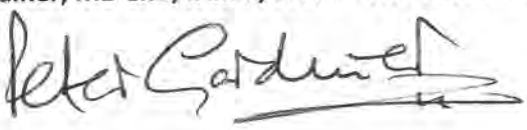
A prospective study conducted at Bologna University enabled a within-subject comparison of the performance of fluciclovine F 18 PET and 11C-choline PET in patients with BCR post radical prostatectomy (N=89). Followup at 1 year was used as the reference standard. Diagnostic performance was comparable for both agents at PSA values above 1 ng/mL, but fluciclovine F 18 imaging showed higher sensitivity in patients with low PSA levels (<1 ng/ml).[10]

For study BED-001 (n=595), data from the prospective RO1 and Bologna studies above were pooled with data from clinical use at two sites in Norway[11] and the pooled data were retrospectively analyzed. Overall, fluciclovine PET/CT scanning detected sites of recurrence in 68% (403/595) of patients. For patients with baseline PSA values in the lowest quartile (<0.79 ng/mL, n=128), 75 patients (59%) were negative with fluciclovine F 18 PET/CT, but 53 (41% of patients) had positive fluciclovine scans; 13 (10%) had prostate bed findings only, and 40 (31%) had extra-prostatic disease. As the location of disease recurrence affects appropriate therapy selection, this finding is highly relevant.

Schreibmann et al[12] incorporated fluciclovine F 18 PET/CT into radiotherapy treatment planning to define prostate bed and lymph node target volumes in 41 patients. Inclusion of the fluciclovine F 18 images changed the planning volumes for 46 abnormalities (83%) of the total 55, with 28(51%) located in the lymph nodes. Use of fluciclovine F 18 in post-prostatectomy radiotherapy planning was feasible and led to augmentation of the target volumes in the majority (30 of 41) of patients studied.

The recent FDA approval of fluciclovine F 18, based on data from 877 subjects including 797 men diagnosed with PCa, will facilitate its broad availability in the US. We thank the NCCN panel for their consideration.

Sincerely, **Peter Gardiner, MB ChB, MRCP, FFPM - Vice President, Medical Affairs**



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