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NCCN Guidelines Panel: Neuroendocrine Tumors

On behalf of Ipsen Biopharmaceuticals, Inc., I respectfully request the *NCCN Neuroendocrine Tumors Panel* to review the enclosed data for recommendation of lanreotide for the management of locoregional unresectable and/or distant metastatic carcinoid tumors and pancreatic neuroendocrine tumors.

Specific Changes: Based on category 1 high-level evidence showing improvement in PFS over placebo in a randomized double-blind placebo-controlled study of lanreotide in patients with gastroenteropancreatic neuroendocrine tumors (CLARINET), we recommend inclusion of lanreotide for the management of locoregional unresectable disease and/or distant metastases, symptomatic and asymptomatic, with low tumor burden or clinically significant tumor burden, for both carcinoid tumors and pancreatic neuroendocrine tumors.

FDA Clearance: Lanreotide is not FDA-approved for the submitted use in the treatment of gastroenteropancreatic tumors. A supplemental New Drug Application seeking an indication for lanreotide (Somatuline® Depot) for the treatment of gastroenteropancreatic neuroendocrine tumors is expected to be submitted to the US FDA by 2Q2014.

Rationale: The CLARINET study results (publication in press*) support the use of lanreotide for the treatment of unresectable or metastatic gastroenteropancreatic neuroendocrine tumors based on the prolonged PFS, i.e. time to progression or death, compared with placebo (HR=0.47; 95% CI, 0.30–0.73; *P*=0.0002).

*The CLARINET data is in press in a peer-reviewed journal. More details are forthcoming regarding the publication date.

The following list of publications is provided in support of the above proposed changes.

1. Caplin ME, Ruszniewski P, Pavel M, et al. Antiproliferative effects of lanreotide autogel in patients with enteropancreatic neuroendocrine tumours: results of CLARINET, a large international phase 3 study. Abstract P578. Presented at the European Congress of Endocrinology, May 2014.
2. Martín-Richard M, Massutí B, Pineda E, et al. Antiproliferative effects of lanreotide autogel in patients with progressive, well-differentiated neuroendocrine tumours: a Spanish, multicentre, open-label, single arm phase II study. *BMC Cancer*. 2013;13:427.
3. Bajetta E, Procopio G, Catena L, et al. Lanreotide autogel every 6 weeks compared with Lanreotide microparticles every 3 weeks in patients with well differentiated neuroendocrine tumors: a Phase III Study. *Cancer*. 2006;107(10):2474-2481.

Sincerely,

Martine George, MD
Interim Vice President Medical and Regulatory Affairs

Addendum
Specific Requests to NCCN Guidelines Panel: Neuroendocrine Tumors

Page	Current language	Recommended change
CARC-6	Asymptomatic, low tumor burden → Observe with markers and scans every 3-12 mo or octreotide	Suggest inclusion of lanreotide based on the high level of evidence [footnote: For tumor control, the CLARINET study used lanreotide Depot 120 mg every 4 weeks.]
PanNET-7	Asymptomatic, low tumor burden, and stable disease → Observe with markers and scans every 3-12 mo	Suggest adding lanreotide in addition to observation [footnote: For tumor control, the CLARINET study used lanreotide Depot 120 mg every 4 weeks.]
PanNET-7	Clinically significant tumor burden → Manage clinically significant symptoms as appropriate → list of therapies	Suggest adding Lanreotide if not already receiving (Category 1) to the list of therapies
MS-10	The potential role of lanreotide in slowing tumor progression was recently evaluated. The CLARINET study randomized 204 patients with locally advanced or metastatic nonfunctioning pancreatic or intestinal neuroendocrine tumors to receive either lanreotide or placebo and followed patients for PFS. Preliminary results from this trial showed that treatment with lanreotide for 2 years resulted in an improvement in PFS over placebo (PFS, not reached vs. 18 months; HR, 0.47; 95% CI, 0.30–0.73; P = .0002). A final report from this study is pending.	The role of lanreotide in slowing tumor progression was evaluated. The CLARINET study randomized 204 patients with locally advanced or metastatic nonfunctioning pancreatic or intestinal neuroendocrine tumors to receive either lanreotide or placebo and followed patients for PFS. Results from this trial showed that treatment with lanreotide for 2 years resulted in an improvement in PFS over placebo (PFS, not reached vs. 18 months; HR, 0.47; 95% CI, 0.30–0.73; P = .0002).
MS-10	Above paragraph falls under section "Somatostatin Analogs for Symptom Control"	Suggest including the above paragraph under a new section titled "Somatostatin Analogs for Disease Control"
MS-17	Although no randomized studies to date have shown an antitumor effect of octreotide in pancreatic neuroendocrine tumors, the PROMID trial showed an improvement in its primary endpoint of time to tumor progression (14.3 vs. 6 months; *P* = .000072) in carcinoid tumors of the midgut. Preliminary results from the CLARINET study, in which 204 patients with gastroenteropancreatic neuroendocrine tumors were randomized to receive treatment with either lanreotide or placebo, showed that treatment with lanreotide was associated with in an improvement in PFS (PFS, not reached vs. 18 months; HR, 0.47; 95% CI, 0.30–0.73; *P* = .0002).	In the CLARINET study, 204 patients with gastroenteropancreatic neuroendocrine tumors, 44% of which had pancreatic neuroendocrine tumors, were randomized to receive treatment with either lanreotide or placebo. The study showed that treatment with lanreotide was associated with an improvement in PFS (PFS, not reached by 96 weeks vs. 18 months; HR=0.47; 95% CI, 0.30–0.73; *P*=0.0002). To date no randomized studies have shown an antitumor effect of octreotide in pancreatic neuroendocrine tumors, the PROMID trial showed an improvement in its primary endpoint of time to tumor progression (14.3 vs. 6 months; *P*=0.000072) in carcinoid tumors of the midgut.