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September 7, 2018

National Comprehensive Cancer Network® (NCCN®)
275 Commerce Drive, Suite 300
Fort Washington, PA 19034

RE: Request for the addition of AZEDRA® (iobenguane I 131) for the unapproved Food and Drug Administration use for the treatment of high-risk unresectable locally advanced or metastatic iobenguane scan-positive tumors, high-risk neuroblastoma, and gastroenteropancreatic neuroendocrine tumors including carcinoid to the NCCN Compendium®.

Dear NCCN:

On behalf of Progenics Pharmaceuticals, Inc., I am writing to request that AZEDRA® (iobenguane I 131) be included in the NCCN Compendium® monograph for the non-Food and Drug Administration (FDA) approved use for the treatment of high-risk unresectable locally advanced or metastatic iobenguane scan-positive tumors, high-risk neuroblastoma, and gastroenteropancreatic neuroendocrine tumors (GEP-NETS) including carcinoid, based on the clinical evidence supporting this use.

For your reference in reviewing this request, I have enclosed the following information:

- A complete request for consideration for iobenguane scan-positive tumors, including clinical evidence for AZEDRA in relapsed/refractory high-risk neuroblastoma and GEP-NETS
- AZEDRA package insert
- Matthay KK, et al. *J Nucl Med*. 2012;53(7):1155-1163
- Matthay KK, et al. *J Nucl Med.* 2001;42(11):1713-1721
- Coleman RE, et al. *Cancer Biother Radiopharm*. 2009;24(4):469-475
- Noto RB, et al. *J Clin Endocrinol Metab*. 2018;103(1):213-220
- A referenced bibliography

AZEDRA is a radioactive therapeutic agent FDA approved for the treatment of adult and pediatric patients 12 years and older with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma (PHEO) or paraganglioma (PARA) who require systemic anticancer therapy (AZEDRA PI).

Treatment of high-risk neuroblastoma is challenging (Applebaum 2017). Neuroblastoma typically occurs in childhood, where the survival prognosis is highly dependent on the child's age and disease stage at diagnosis (Tolbert 2018). Symptoms typically reflect the location of the primary tumor and may include Horner syndrome, proptosis, abdominal pain, and back pain (Tolbert 2018). While therapies for this pediatric neoplasm of the sympathetic nervous system with diverse symptomatology have improved, fewer than 50% of patients with high-risk disease will survive long term (Applebaum 2017).

GEP-NETS are a heterogeneous collection of neuroendocrine neoplasms that often present at an advanced stage with poor associated outcomes (Ezziddin 2006; Kos-Kudła 2017). GEP-NETS commonly affect organs of the gastrointestinal tract (Ezziddin 2006; Kos-Kudła 2017; Pinchot 2008; Zeutenhorst 2005). Surgical intervention is the only curative therapy for these tumors; however, management of metastases, which occur in the liver of as many as 75% of patients, remains challenging (Kos-Kudła 2017; Pinchot 2008; Coleman 2009).

Phase 1 and 2 studies of AZEDRA in metastatic carcinoid and relapsed/refractory high-risk neuroblastoma are summarized in the enclosed document. Considering this high unmet need in both relapsed/refractory high-risk neuroblastoma and GEP-NETS, I respectfully request adding these indications to the AZEDRA NCCN Compendium® monograph.

I appreciate the opportunity to present these data for consideration by the NCCN Compendium® editorial staff. If you have any questions or require additional information, please do not hesitate to contact me at (646) 975-2512 or at smahmood@progenics.com. Thank you for your assistance with this process.

Sincerely,

Syed Mahmood, MD
Vice President, Medical Affairs
Progenics Pharmaceuticals, Inc.
(646) 975-2512
One World Trade Center, New York, NY 10007

Enclosures:

Clinical review of AZEDRA in iobenguane scan-positive tumors, including relapsed/refractory high-risk neuroblastoma and GEP-NETS

AZEDRA package insert

Matthay KK, et al. *J Nucl Med*. 2012;53(7):1155-1163

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