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September 11, 2018

NCCN Staff

RE: Request for the addition of AZEDRA® (iobenguane I 131) for the treatment of adult and pediatric patients 12 years and older with iobenguane scan-positive, unresectable, locally advanced, or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy to NCCN drug compendia

Dear NCCN Staff:

On behalf of Progenics Pharmaceuticals, Inc., I am writing to request that the use of AZEDRA® (iobenguane I 131), a radioactive therapeutic agent approved by the Food and Drug Administration (FDA) 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) be created and added to the LexiDrugs compendium for this therapy 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, including clinical evidence for AZEDRA in PHEO/PARA
- AZEDRA package insert and FDA approval letter
- Bibliography of other published studies, including poster presentations and abstracts, of AZEDRA in PHEO/PARA as well as clinical practice guidelines of PHEO/PARA
- Coleman RE, et al. *Cancer Biother Radiopharm*. 2009;24(4):469-475
- Jimenez C, et al. Oral presentation at: ENDO 2018; March 17-20, 2018; Chicago, IL
- Noto RB, et al. *J Clin Endocrinol Metab.* 2018;103(1):213-220
- Pryma DA, et al. Oral presentation at: 2018 ASCO Annual Meeting; June 1-5, 2018; Chicago, IL

PHEO and PARA comprise a very rare and diverse subset of neuroendocrine tumors originating from neural crest-derived chromaffin cells of the adrenal medulla (PHEO) and the extra-adrenal sympathetic and parasympathetic paraganglia (PARA) (Carrasquillo 2016; Lefebvre 2014). Symptoms are often vague and vary widely, affecting the cardiovascular, renal, gastrointestinal, cerebrovascular, and ocular systems, and can ultimately contribute to multisystem organ failure (Lefebvre 2014; Jimenez 2013; Baudin 2014; Phan 2014). These symptoms result in prolonged time from onset to diagnosis, resulting in patients often presenting with metastatic disease. If left untreated, metastatic PHEO/PARA results in poor overall survival rates, estimated at 12% to 60% over five years (Ayala-Ramirez 2012; Gunawardane 2017; Park 2011).

Historically, a major unmet medical need in metastatic/malignant or unresectable PHEO/PARA has been the lack of a defined standard of care included in the treatment guidelines. In patients with no symptoms or slowly progressing disease, first-line management has been watch and wait; approximately 50% of therapy-naïve patients exhibit no or minimal disease progression one year after initial diagnosis (Roman-Gonzalez 2017; Hescot 2013). In watch and wait, clinical and radiographic monitoring is conducted every two to three months after the initial diagnosis, is progressively increased to every six months, and then is conducted once every year (Baudin 2014). In more advanced cases, the presence of uncontrolled hormone- or tumor-related symptoms, high tumor burden, or significant radiographic progression as defined by Response Evaluation Criteria in Solid Tumor (RECIST) justifies therapeutic intervention. However, prior to the approval of AZEDRA, there were no FDA-approved therapies for metastatic, locally advanced, or

unresectable PHEO/PARA. Treatment options include conventional I 131 MIBG, systemic chemotherapy, and molecular-targeted therapies, as well as nondrug modalities such as surgery and external beam radiotherapy (Gunawardane 2017). Notably, none of these therapies are without limitations, and alpha-blockade is often required (Fishbein 2016). In contrast, AZEDRA, is now the only FDA-approved therapy for this patient population.

The pivotal trial for AZEDRA is the largest prospective study of patients with advanced PHEO/PARA to date. It included 81 patients who were aged 12 years and older; MIBG avid; on a stable antihypertensive agent for ≥30 days; and either ineligible for curative surgery, failed prior therapy, or were not candidates for chemotherapy (Pryma 2018). This was a phase 2, prospective, multicenter, open-label, single-arm trial where 74 patients received a dosimetry dose, 68 patients received at least one therapeutic dose, and 50 patients received two therapeutic doses of AZEDRA (Pryma 2018). The primary endpoint in the pivotal trial was the proportion of patients who experienced a clinical benefit, as defined by a reduction of all antihypertensive medication by ≥50% for at least six months (AZEDRA PI). The primary endpoint was met by 25% (95% confidence interval [CI]: 16%, 37%) of all patients who received at least one therapeutic dose, achieving prespecified success criteria. Clinical benefit was achieved in 32% (95% CI: 21%, 46%) of patients who received two therapeutic doses (Pryma 2018).

Patients receiving the full AZEDRA regimen experienced extended overall survival compared to patients treated with only one dose. Patients experienced a median overall survival of 44 months when completing the full therapeutic regimen (n=50) compared to 18 months in patients receiving one therapeutic dose (n=18). Comparable survival rates were seen in patients irrespective of the presence or absence of lung or liver metastases (Pryma 2018).

The safety profile of AZEDRA is consistent with other systemic anticancer therapies; the most common (>30%) adverse reactions (all grades) are lymphopenia (96%), anemia (93%), thrombocytopenia (91%), increased international normalized ratio (INR) (85%), neutropenia (84%), nausea (78%), fatigue (71%), vomiting (58%), increased blood alkaline phosphatase (53%), increased aspartate aminotransferase (AST) (50%), dry mouth (48%), increased alanine aminotransferase (ALT) (43%), sialadenitis (39%), dizziness (34%), and headache (32%) (AZEDRA PI).

AZEDRA is administered intravenously (IV); the dosimetric dose is 185 to 222 MBq (5–6 mCi) in patients weighing >50 kg and 3.7 MBq/kg (0.1 mCi/kg) in patients weighing ≤50 kg (AZEDRA PI). An initial dosimetry test is performed to personally optimize AZEDRA treatment for each patient. Three whole-body scans enable physicians to confirm the individual therapeutic dose. The recommended AZEDRA therapeutic dose is based on body weight and reduced, if necessary, based on the dosimetry data. Administer a total of two therapeutic doses IV a minimum of 90 days apart. The therapeutic dose is 18,500 MBq (500 mCi) in patients weighing >62.5 kg and 296 MBq/kg (8 mCi/kg) in patients weighing ≤62.5 kg (AZEDRA PI). Please refer to prescribing information for information on determining if a dose reduction is needed based on critical organ limits or adverse reactions (AZEDRA PI).

AZEDRA has a safety profile that is consistent with other systemic anticancer therapies and offers an efficacious treatment option to adult and pediatric patients aged 12 years and older with iobenguane scan-positive, unresectable, locally advanced, or metastatic PHEO/PARA who require systemic anticancer therapy and should be made available to patients without restriction to those who are afflicted with this rare disorder. I respectfully request creating a monograph for this labeled indication to the NCCN compendium.

AZEDRA selectively targets a well-described characteristic feature of PHEO/PARA—the norepinephrine transporter—to irreversibly damage tumor cells (Barrett 2010). The Ultratrace® manufacturing process results in a high-specific-activity iobenguane I 131 (AZEDRA) radioactive therapeutic agent compared to methods which produce conventional I 131 iobenguane that is predominantly nontherapeutic (Coleman 2009). Conventional I 131 iobenguane (also known as MIBG) contains only 1% active therapeutic molecules compared to AZEDRA, which contains over 99% (Coleman 2009). Nontherapeutic MIBG can compete with active molecules for uptake, storage, and retention in tumor cells (Barrett 2010; Coleman 2009).

I appreciate the opportunity to present these data for consideration by the NCCN 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,

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Enclosures:

Clinical review of PHEO/PARA and AZEDRA

AZEDRA package insert

Bibliography of other published studies, including poster presentations and abstracts

Coleman RE, et al. *Cancer Biother Radiopharm*. 2009;24(4):469-475

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