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Name: Dr. Syed Mahmood, MD, Vice President, Medical Affairs, Progenics Pharmaceuticals, Inc.
Company: Progenics Pharmaceuticals, Inc.
Address: 1 World Trade Center, Floor 47 Suite J, New York, NY 10019
Email: smahmood@progenics.com Business: +1-646-975-2512
NCCN Guidelines Panel Neuroendocrine Cancer

On behalf of Progenics Pharmaceuticals, Inc., we respectfully request the NCCN Neuroendocrine Cancer Panel to review the enclosed data supporting the use of high-specific-activity (HSA) iobenguane I 131 (AZEDRA®) for the treatment of adult and pediatric patients 12 years or older with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy.

Approval status:
An NDA for HSA iobenguane I 131 has been submitted with a PDUFA date of July 30, 2018. If approved, HSA iobenguane I 131 would be the first and only U.S. Food and Drug Administration (FDA)-approved therapy for the treatment of adult and pediatric patients 12 years or older with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma (PHEO/PGL) who require systemic anticancer therapy.

Specific change requested: We request inclusion of HSA iobenguane I 131 to the list of therapeutic options available for patients with MIBG-avid tumors, and especially in the evaluation of and primary treatment of PHEO/PGL patients with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy.

Disease background:
PHEO/PGL are rare diseases. PHEO/PGL tumors may secrete catecholamines and other neuroendocrine biomarkers that could be measured to assess response to treatment. Approximately 10-35% of PHEO/PGLs are metastatic and/or locally-invasive at initial diagnosis. 5 year overall survival rate of patients with metastatic PHEO/PGLs is as low as 12%. Tumor progression is the most frequent cause of death and up to 30% of metastatic PHEO/PGL deaths result from catecholamine related complications. There are no FDA-approved therapies for the treatment of unresectable, locally advanced or metastatic PHEO/PGL who require systemic anticancer therapy. Non-approved and most widely studied therapeutic options include, chemotherapy regimens with cyclophosphamide, vincristine, and dacarbazine (CVD), and conventional low-specific-activity I-131 MIBG therapy at high doses and HSA iobenguane I 131.[1-5]

Rationale:
We believe that clinical studies thus far indicate that HSA iobenguane I 131 is a tolerable, feasible, and effective radiopharmaceutical for the treatment of unresectable, locally advanced or metastatic PHEO/PGL who require systemic anticancer therapy, as well as, based on clinical trial evidence, a treatment option in patients with refractory neuroblastoma, and request consideration of the following data.

HSA iobenguane I 131 is a high-specific-activity formulation of iodine-131 meta-iodobenzylguanidine (AZEDRA) that consists almost entirely of labeled I-131 MIBG molecules allowing for lower doses of unlabeled MIBG to be administered. Of note, the unlabeled MIBG is widely known to contribute directly to cardiovascular sequalae.

HSA iobenguane I 131 holds Breakthrough Therapy designation from the FDA and Orphan Drug statuses from both the FDA and European Medicines Agency, as well as Fast Track designation and was granted Priority Review by the FDA. Our NDA is based on our pivotal Phase 2 open-label, multicenter trial conducted under a Special Protocol Assessment (SPA) agreement with the FDA.

HSA iobenguane I 131 was evaluated in 96 patients with PHEO/PGL and 22 patients with other malignancies who received at least a dosimetry dose of HSA iobenguane I 131. Three clinical studies established the safety and efficacy of HSA iobenguane I 131 in patients for the treatment of unresectable, locally advanced or metastatic PHEO/PGL who require systemic anticancer therapy.[6-10]

The first, a phase 1 dosimetry study (IB11) evaluated safety, radiation dosimetry, distribution, and metabolism of HSA iobenguane I 131 in adult patients with metastatic neuroendocrine tumors including PHEO/PGL (Total n=11, PHEO/PGL n= 4).[6]

The second, a phase 1 open label, multi-center, single-arm dose-escalation study (IB12), assessed the maximum tolerated therapeutic dose of HSA iobenguane I 131, dosimetry, safety and preliminary efficacy of HSA iobenguane I 131 in adult patients with metastatic and/or recurrent PHEO/PGL (n=21).[7]

The third, a phase 2, open-label, multi-center, single-arm, efficacy and long-term safety study (IB12B) evaluated patients ages 12 and older with iobenguane scan-positive, unresectable, locally advanced or metastatic PHEO/PGL who require systemic anticancer therapy (n=74). Results from this pivotal study demonstrates that the primary endpoint of the study was achieved, which evaluated the proportion of patients who achieved a 50% or greater reduction in all antihypertensive medication for at least six months. The achievement of the endpoint was determined by the lower limit of the two-sided 95% confidence interval, which needed to be above 10%, demonstrating the ability of HSA iobenguane I 131 to improve blood pressure control and reduce the use of antihypertensive medications in PHEO/PGL. Furthermore, results from the secondary endpoints, including objective tumor response, showed benefit in both patients who met criteria as responders on the primary outcome and those who did not. Of the 64 RECIST evaluable patients who received at least one therapeutic dose of HSA iobenguane I 131, 92% of subjects achieved disease control. And, of those patients who received two therapeutic doses, 30% achieved a partial response and 68% had stable disease, for a notable, combined 98% disease control. Of note, patients treated with HSA iobenguane I 131 demonstrated a median overall survival of 36.7 months from first HSA iobenguane I 131 therapeutic dosing in the overall study population, with 48.73 months among patients who received two therapeutic doses. Also of note, survival data in this population in literature show a 5-year survival rates as low as 12%. Pooled PHEO/PGL safety data from IB11, IB12 and IB12B reveals that the most common (≥ 10%) severe (Grade 3-4) adverse reactions were leukopenia (46%), thrombocytopenia (41%), neutropenia (44%), fatigue (19%), anemia (18%) and nausea (10%).[8,9]

In addition, HSA iobenguane I 131 has been evaluated in children as young as 3 years of age with high-risk relapsed or refractory neuroblastoma in collaboration with the New Advances in Neuroblastoma Therapy (NANT) consortium. In a Phase 2a, open-label, dose-escalating, multicenter study (IB13) of HSA iobenguane I 131 in 15 patients with MIBG-avid relapsed/refractory high-risk neuroblastoma, eligible patients received a diagnostic imaging dose of HSA iobenguane I 131 (1-5 mCi) followed by therapeutic dosing, which began at 12.0 mCi/kg (444 MBq/kg) and rising to 21.0 mCi/kg (777 MBq/kg). On independent review, 1 complete response (CR) and 3 partial response (PR). Additionally, 6 patients had stable disease (SD) and 1 patient had a mixed response (MR). The response rates were greater at the higher dose levels, with 3 of 7 patients at 666 MBq/kg with CR or PR and another with MR. Of the 4 patients that had progressive disease (PD), 2 were adults. In general, the safety profile of HSA iobenguane I 131 is similar to the PHEO/PGL population.[10]

We thank the NCCN panel for their consideration.

Faithfully,

Syed Mahmood, MD
Vice President, Medical Affairs
Progenics Pharmaceuticals, Inc
646.975-2512
One World Trade Center, New York, NY 10007

Progenics® Pharmaceuticals

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