pralsetinib (Gavreto™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO220

Description

Pralsetinib (Gavreto) is an orally administered kinase inhibitor of RET.

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
pralsetinib (Gavreto)	100 mg capsules	RET Fusion-Positive Non-Small Cell Lung Cancer; RET-Mutant Medullary Thyroid Cancer; RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory	120 capsules/30 days

Initial Evaluation

I. **Pralsetinib (Gavreto)** is considered investigational when used for all indications, including but not limited to Non-Small Cell Lung Cancer (NSCLC) and Thyroid Cancer.

Renewal Evaluation

I. N/A

Supporting Evidence

I. RET, a transmembrane receptor protein, is present at the surface of several tissue types. Alterations include fusions and point mutations – both are oncogenic drivers. Pralsetinib (Gavreto) is the second FDA-approved RET-targeted therapy, joining selpercatinib (Retevmo).

II. RET fusion-positive NSCLC, advanced or metastatic: First-line treatments include cabozantinib (Cometriq®) or vandetanib (Caprelsa®) (both off-label for lung cancer), combinations of platinum-based chemotherapy, anti-PD-1/PD-L1 therapy, pemetrexed (Alimta®), and bevacizumab. In the second-line setting, additional options include various immunotherapy and chemotherapy treatments (e.g., taxanes, gemcitabine); however, all of these therapies show poorer outcomes in this population vs. non-RET mutated NSCLC.
    - NCCN guidelines include pralsetinib (Gavreto) and selpercatinib (Retevmo) as preferred first-line and subsequent-line therapy after other options have failed (recommendation

Category 2a). Cabozantinib (Cometriq) and vandetanib (Caprelsa) are listed as useful in certain circumstances, with a Category 2a and 2b recommendation, respectively. ESMO guidelines mention pralsetinib (Gavreto) and selpercatinib (Retevmo) for RET-mutated NSCLC; however, given the limited data, enrollment in clinical trials is encouraged.

III. RET-mutant MTC, advanced or metastatic: Systemic treatment may be warranted for high volume, symptomatic or progressive MTC. General treatment options include cabozantinib (Cometriq) or vandetanib (Caprelsa).
   - NCCN guidelines recommend cabozantinib (Cometriq) and vandetanib (Caprelsa) as Category 1 preferred options. Selpercatinib (Retevmo) is listed as a Category 2a preferred therapy for those with RET-mutations in both the locoregional, symptomatic, and unresectable setting, as well as the recurrent or persistent settings. Enrollment in clinical trial has a Category 2a recommendation.

IV. RET fusion-positive thyroid cancer: In persistent/recurrent or metastatic disease, RAI is recommended. In those not amenable to RAI, general treatment options include lenvatinib (Lenvima®) or sorafenib (Nexavar®).
   - NCCN guidelines recommend lenvatinib (Lenvima) and sorafenib (Nexavar) as Category 2a with lenvatinib (Lenvima) preferred. Selpercatinib (Retevmo) is the preferred therapy for RET fusion-positive disease, Category 2a.

V. Pralsetinib (Gavreto) has not been included in treatment guidelines for thyroid cancer.

VI. Pralsetinib (Gavreto) is being evaluated in one Phase 1/2, dose expansion and escalation, multi-cohort, open-label, single-arm trial. Interim results showed potential antitumor activity via overall response rate (ORR) and duration of response (DoR). These indications were approved under the accelerated pathway and continued approval may be contingent upon verification of clinical benefit in confirmatory trials. The primary outcome is ORR, and the secondary outcomes include DoR and proportion of patients with DoR six months or greater.

VII. For RET fusion-positive NSCLC: Patients were advanced or metastatic and were either treatment naïve or progressed on platinum-based chemotherapy. For RET-mutant MTC, patients were either treatment naïve or progressed on cabozantinib (Cometriq) or vandetanib (Caprelsa). All patients had progressed on standard of care for RET-fusion-positive TC.

Clinical Efficacy in Pretreated Patients			
Outcome	**RET Fusion+ NSCLC (n=87)**	**RET-Mutant MTC (n=55)**	**RET Fusion-Positive TC (n=9)**
ORR (%)	57% (46, 68)	60% (46, 73)	89% (52, 100)
CR (%)	5.7%	1.8%	0
PR (%)	52%	58%	89%
DoR (mo)	NR (15.2-NE)	NR (15.1, NE)	NR (NE, NE)
DoR ≥ 6 mo (%)	80%	79%	100%
Clinical Efficacy in Treatment-Naïve Patients			
Outcome	**RET Fusion+ NSCLC (n=27)**	**RET-Mutant MTC (n=29)**	**RET Fusion-Positive TC***
ORR (%)	70% (50, 86)	66% (46, 82)	N/A
CR (%)	11%	10%	
PR (%)	59%	55%	
DoR (mo)	9 (6.3-NE)	NR (NE, NE)	
DoR ≥ 6 mo (%)	58%	84%	

*All patients were refractory to standard therapy.

VIII. The quality of the evidence is considered low given the open-label and single-arm trial design and small sample size; thus, true medication efficacy remains uncertain given the nature of observational data. Additionally, outcomes such as ORR and DoR have not been correlated with clinically meaningful outcomes such as improved survival or quality of life.

IX. Phase 3 trial, AcceleRET, is planned to evaluate pralsetinib (Gavreto) in advanced or metastatic, RET fusion-positive NSCLC versus platinum-based chemotherapy. It will be evaluated in an open-label, randomized trial for first-line metastatic systemic therapy. Outcomes of interest include PFS, OS, time to intracranial progression, and quality of life. This international trial has a target enrollment of 250 patients, with an estimated completion date of 2024.

X. Safety data is based on a pooled population of 438 patients. Common adverse events (AE) that occurred ≥15% or more of the population: fatigue, constipation, musculoskeletal pain, hypertension, edema, diarrhea, dry mouth, cough, and pneumonia. Serious AE that occurred ≥2%: pneumonia, sepsis, UTI, pyrexia, increased ALT/AST, and phosphatase, and decreased lymphocytes, neutrophils, hemoglobin, phosphate, calcium, sodium, and platelets. Fatal AE occurred in 5% of patients (pneumonia and sepsis) in the NSCLC cohort. Warnings and precautions: interstitial lung disease, hypertension, hepatotoxicity, hemorrhage, tumor lysis syndrome, impaired wound healing, and embryo-fetal toxicity.

XI. Dose reductions due to AE occurred in up to 67% of patient, which varied by cohort. Dose reductions occurred in up to 44%, and permanent discontinuation rate in up to 15%. The true safety profile of pralsetinib (Gavreto) remains unknown given the observational evaluation.

Investigational or Not Medically Necessary Uses

I. Pralsetinib (Gavreto) has not yet been sufficiently studied for safety and efficacy for any condition.

References

1. Gavreto [Prescribing Information]. Blueprint Medicines Corporation. Cambridge, MA. December 2020.
2. Retevmo [Prescribing Information]. Eli Lilly and Company. Indianapolis, IN. May 2020.
3. Adeniran AJ, Ahu Z, Gandhi M, et al. Correlation between genetic alterations and microscopic features, clinical manifestations, and prognostic characteristics of thyroid papillary carcinomas. Am J Surg Pathol. 2006. 30(2): 216-222.
4. Drilon A, Hu ZI, Lai GGY, Tan DSW. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. Nat Rev Clin Oncol. 2018a Mar;15(3):151-67.
5. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Treatment Guidelines V8.2020. September 21, 2020. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx.
6. European Society for Medical Oncology. Metastatic non-small-cell lung cancer. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 15, 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2021