PDL DRUG REVIEW

Proprietary Name: Gavreto®
Common Name: pralsetinib
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Retevmo	Non-Recommended with Conditions

Summary

Pharmacology/Usage: Pralsetinib, the active ingredient of Gavreto®, is an oral receptor tyrosine kinase inhibitor. It is a kinase inhibitor of wild-type *RET* and oncogenic *RET* fusions.

Indication: For the treatment of:

- **Metastatic *RET* Fusion-Positive Non-Small Cell Lung Cancer (NSCLC)**- For adults with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.
- ***RET*-Mutant Medullary Thyroid Cancer (MTC)**- For adults and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant MTC who require systemic therapy.
- ***RET* Fusion-Positive Thyroid Cancer**- For adults and pediatric patients 12 years of age and older with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

There is no pregnancy category for this product; however, the risk summary indicates that based on findings from animal studies and its mechanism of action, Gavreto® can cause fetal harm when administered to a pregnant woman. There are no available data on use in pregnant women to inform drug-associated risk. Advise pregnant women of the potential risk to the fetus. Pregnancy testing is recommended for females of reproductive potential before starting Gavreto®. Advise females of reproductive potential to use effective non-hormonal contraception during treatment and for 2 weeks after the final dose. Gavreto® may render hormonal contraceptives ineffective. In addition, advise males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the final dose. The safety and efficacy of use in the pediatric population have not been established with *RET* fusion-positive NSCLC or in pediatric patients younger than 12 years old with *RET*-mutant MTC or *RET* fusion-positive thyroid cancer.

Dosage Form: Capsules: 100mg

Recommended Dosage: Select patients for treatment with Gavreto® based on the presence of a *RET* gene fusion (NSCLC or thyroid cancer) or *RET* gene mutation (MTC). Information on FDA-approved tests for *RET* gene fusion (NSCLC) is available at http://www.fda.gov/CompanionDiagnostics. An FDA-approved test for the detection of *RET* gene fusion (thyroid cancer) and *RET* gene mutations is not currently available.

Take 400mg PO QD on an empty stomach until disease progression or until unacceptable toxicity. There should be no food intake for at least 2 hours before and at least one hour after taking Gavreto®. If a dose of Gavreto® is missed,

it can be taken as soon as possible on the same day. Resume the regular daily dose schedule for Gavreto® the next day. Do not take an additional dose if vomiting occurs after Gavreto® but continue with the next dose as scheduled.

Dose reductions and dosage modifications may be required for adverse reactions, such as interstitial lung disease (ILD)/pneumonitis, hypertension, hepatotoxicity, hemorrhagic events, or other adverse reactions. Refer to the prescribing information for further information. In addition, while dose adjustments are not required with mild hepatic impairment, Gavreto® use has not been studied in patients with moderate or severe hepatic impairment. Mild and moderate renal impairment had no effect on the exposure of pralsetinib, but use has not been studied in patients with severe renal impairment.

Drug Interactions: Avoid coadministration of Gavreto® with strong CYP3A inhibitors.

Avoid coadministration of Gavreto® with combined P-gp and strong CYP3A inhibitors. If coadministration with a combined P-gp and strong CYP3A inhibitor cannot be avoided, reduce the Gavreto® dose. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume Gavreto® at the dose taken prior to starting the combined P-gp and strong CYP3A inhibitor. Refer to the prescribing information for further information.

Avoid coadministration of Gavreto® with strong CYP3A inducers. If coadministration cannot be avoided, increase the starting dose of Gavreto® to double the current Gavreto® dosage starting on day 7 of coadministration of Gavreto® with the strong CYP3A inducer. After the inducer has been discontinued for at least 14 days, resume Gavreto® at the dose taken prior to initiating the strong CYP3A inducer.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Gavreto®) for grades 1-4. Please note that there was no placebo data in the prescribing information to compare with.* The most frequently reported adverse events included fatigue (35%), pyrexia (20%), edema (20%), constipation (35%), diarrhea (24%), dry mouth (16%), musculoskeletal pain (32%), hypertension (28%), cough (23%), and pneumonia (17%). Laboratory abnormalities included increased AST (74%), increased ALT (49%), increased alkaline phosphatase (42%), decreased calcium, corrected (39%), decreased albumin (36%), decreased phosphate (35%), increased creatinine (33%), decreased sodium (29%), increased potassium (26%), decreased lymphocytes (56%), decreased neutrophils (61%), decreased hemoglobin (58%), and decreased platelets (27%).

Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with Gavreto®. Pneumonitis occurred in 10% of patients who received Gavreto®. Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold Gavreto® and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD. Withhold, reduce dose or permanently discontinue Gavreto® based on severity of confirmed ILD.

Hypertension occurred in 29% of patients. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Do not start Gavreto® in patients with uncontrolled hypertension. Optimize blood pressure prior to starting Gavreto®. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Gavreto® based on the severity.

Serious hepatic adverse reactions occurred in 2.1% of patients treated with Gavreto®. The median time to first onset for increased AST was 15 days (range 5 days to 1.5 years) and increased ALT was 22 days (range 7 days to 1.7 years). Monitor AST and ALT prior to starting Gavreto®, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Gavreto® based on severity.

Serious, including fatal, hemorrhagic events can occur with Gavreto®. Permanently discontinue Gavreto® in patients with severe or life-threatening hemorrhage.

Cases of tumor lysis syndrome (TLS) have been reported in patients with medullary thyroid carcinoma receiving Gavreto®. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Thus, Gavreto® has the potential to adversely affect wound healing. Withhold Gavreto® for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Gavreto® after resolution of wound healing complications has not been established.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Blueprint Medicines Corp.

Analysis: The efficacy of Gavreto® was assessed in patients with *RET* fusion-positive NSCLC in a multicenter, non-randomized, open-label, multi-cohort study (ARROW). The study enrolled, in separate cohorts, patients with metastatic *RET* fusion-positive NSCLC who had progressed on platinum-based chemotherapy and treatment-naïve patients with metastatic NSCLC. Patients with asymptomatic CNS metastases, including patients with stable or decreasing steroid use within 2 weeks prior to study entry, were enrolled. All patients received Gavreto® daily until disease progression or unacceptable toxicity. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as assessed by a blinded independent central review (BICR) per RECIST v1.1

Efficacy was assessed in patients with *RET fusion-positive NSCLC with measurable disease who were previously treated with platinum chemotherapy* enrolled into a cohort (N=87). The median age of this cohort was 60 years, while 49% were female, 53% were white, 99% had metastatic disease, and 43% had either a history of or current CNS metastasis. In addition, 94% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status 0-1 and 6% had an ECOG performance status of 2. Patients received a median of 2 prior systemic therapies (range 1-6) and 52% received prior radiation therapy. Efficacy results for *RET* fusion-positive NSCLC patients who received prior platinum-based chemotherapy can be seen in the table below, which was adapted from the prescribing information.

Efficacy Parameter	Gavreto® (N=87)
Overall Response Rate (ORR)	57%
Complete Response (CR)	5.7%
Partial Response	52%
Duration of Response (DOR)	N=50
Median, months	Not estimable
Patients with DOR ≥6 months	80%

For the 39 patients who received an anti-PD-1 or anti-PD-L1 therapy, either sequentially or concurrently with platinum-based chemotherapy, an exploratory subgroup analysis of ORR was 59% and the median DOR was not reached.

Among the 87 patients with *RET* fusion-positive NSCLC, 8 had measurable CNS metastases at baseline as assessed by BICR. No patients received radiation therapy (RT) to the brain within 2 months prior to study entry. Responses in intracranial lesions were observed in 4 of these 8 patients, including 2 patients with a CNS complete response; 75% of responders had a DOR of ≥6 months.

Efficacy was assessed in patients with *treatment-naïve RET fusion-positive NSCLC with measurable disease* (N=27). The median age of included adults was 65 years (range 30 to 87), while 52% were female, 59% were white, 100% had metastatic disease with 37% having either a history of or current CNS metastasis. In addition, 96% of the patients had an ECOG performance status of 0-1. Efficacy results for treatment-naïve *RET* fusion-positive NSCLC can be seen in the table below, which was adapted from the prescribing information.

Efficacy Parameter	Gavreto® (N=27)
Overall Response Rate (ORR)	70%
Complete Response (CR)	11%
Partial Response	59%
Duration of Response (DOR)	N=19
Median, months	9.0
Patients with DOR ≥6 months	58%

The efficacy of Gavreto® was assessed in patients with *RET*-mutant MTC in a multicenter, open-label, multi-cohort study (ARROW). Efficacy was assessed in patients with *RET-mutant metastatic MTC previously treated with cabozantinib or vandetanib* (or both). The median age of included patients (N=55) was 59 years (range 25 to 83), while 69% were male, 78% were white, 95% had an ECOG performance status of 0-1, 5% had an ECOG performance status of 2, and 7% had a history of CNS metastases. In addition, patients had received a median of 2 prior therapies (range 1-7). Efficacy results can be seen in the table below, which was adapted from the prescribing information.

Efficacy Parameter	Gavreto® (N=55)
Overall Response Rate (ORR)	60%
Complete Response (CR)	1.8%
Partial Response	58%
Duration of Response (DOR)	N=33
Median, months	Not reached
Patients with DOR ≥6 months	79%

The efficacy of Gavreto® was also assessed in patients with *RET-mutant advanced MTC who were cabozantinib and vandetanib treatment-naïve* (N=29). The median age of included adults was 61 years (range 19 to 81 years), while 72% were male, 76% were white, 100% had an ECOG performance status of 0-1, 97% had metastatic disease, and 14% had a history of CNS metastases. In addition, 28% had received up to 3 lines of prior systemic therapy. Efficacy results can be seen in the table below, which was adapted from the prescribing information.

Efficacy Parameter	Gavreto® (N=29)
Overall Response Rate (ORR)	66%
Complete Response (CR)	10%
Partial Response	55%
Duration of Response (DOR)	N=19
Median, months	Not reached
Patients with DOR ≥6 months	84%

The efficacy of Gavreto® was assessed in *RET fusion-positive metastatic thyroid cancer patients* in a multicenter, open-label, multi-cohort study (ARROW). All patients with *RET* fusion-positive thyroid cancer were required to have

disease progression following standard therapy, measurable disease by RECIST version 1.1, and have *RET* fusion status as detected by local testing. The median age of included adults was 61 years (range 46 to 74 years), while 67% were male, 78% were white, 100% had ECOG performance status 0-1, 100% had metastatic disease, and 56% had a history of CNS metastases. In addition, patients had received a median of 2 prior therapies (range 1-8), with prior systemic treatments including prior radioactive iodine (100%) and prior sorafenib and/or lenvatinib (56%). Results can be seen in the table below, which was adapted from the prescribing information.

Efficacy Parameter	Gavreto® (N=9)
Overall Response Rate (ORR)	89%
Complete Response (CR)	0%
Partial Response	89%
Duration of Response (DOR)	N=8
Median, months	Not reached
Patients with DOR ≥6 months	100%

Place in Therapy: Gavreto® is oral tyrosine kinase inhibitor indicated for the treatment of adults with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test. It is also indicated for *RET*-mutant medullary thyroid cancer (in adults and pediatric patients 12 years and older) who require systemic therapy and for *RET* fusion-positive thyroid cancer (in adults and pediatric patients 12 years and older) who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trial(s). In a single-arm, open-label, multi-cohort study that included patients taking Gavreto®, the overall response rate for *RET* fusion-positive NSCLC patients who received prior platinum-based chemotherapy was 57%, while for treatment-naïve *RET* fusion-positive NSCLC patients the overall response rate was 70%. The overall response rate for *RET*-mutant MTC patients previously treated with cabozantinib or vandetanib was 60%, while in cabozantinib and vandetanib-naïve *RET*-mutant MTC patients the overall response rate was 66%. Last, the overall response rate for *RET* fusion-positive thyroid cancer patients was 89% (but this was a very small sample size of 9 patients).

It is recommended that Gavreto® should be non-recommended in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Gavreto [package insert]. Cambridge, MA: Blueprint Medicines Corp; 2020.