Dosing & Administration Guide

GAVRETO™—the **only once-daily targeted RET therapy** for patients with RET+ metastatic NSCLC and advanced thyroid cancers.[1]

Learn more about managing treatment with **GAVRETO.**

NSCLC=non–small cell lung cancer; RET=rearranged during transfection.

INDICATIONS

GAVRETO™ (pralsetinib) is indicated for the treatment of:

- Adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
- Adult and pediatric patients 12 years of age and older with 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 trials.

SELECT SAFETY INFORMATION

Interstitial Lung Disease (ILD)/Pneumonitis occurred in 10% of patients who received GAVRETO, including 2.7% with Grade 3/4, and 0.5% with fatal reactions. 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 (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD.

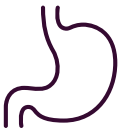
Please see additional Select Safety Information throughout, and click here to see the full Prescribing Information for GAVRETO.

The only once-daily RET inhibitor[1]

Recommended starting dose: 400 mg once daily

Four 100-mg capsules

Bottle and capsules are not actual size.



Patients should take GAVRETO on an empty stomach (no food intake for at least 2 hours before and at least 1 hour after taking GAVRETO).

- Continue treatment until disease progression or until unacceptable toxicity
- 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
- Advise patients not to take an additional dose if vomiting occurs after taking GAVRETO, but continue with the next dose as scheduled
- Select patients for treatment with GAVRETO based on the presence of a RET gene fusion

Select patient counseling information

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Interstitial Lung Disease (ILD)/ Pneumonitis: Advise patients to contact their healthcare provider if they experience new or worsening respiratory symptoms.

Drug Interactions: Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products.

SELECT SAFETY INFORMATION

Hypertension occurred in 29% of patients, including Grade 3 hypertension in 14% of patients. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating 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.

Dosage modifications with GAVRETO[1]

GAVRETO is available in 100-mg capsules, giving you the opportunity to modify dosage based on individual patient needs

First reduction:
300 mg once daily

Second reduction:
200 mg once daily

Final reduction:
100 mg once daily

Capsules are not actual size.

Permanently discontinue GAVRETO in patients who are unable to tolerate 100 mg taken orally once daily.

Select patient counseling information

Hypertension: Advise patients that they will require regular blood pressure monitoring and to contact their healthcare provider if they experience symptoms of increased blood pressure or elevated readings.

Hepatotoxicity: Advise patients that hepatotoxicity can occur and to immediately contact their healthcare provider for signs or symptoms of hepatotoxicity.

Hemorrhagic Events: Advise patients that GAVRETO may increase the risk for bleeding and to contact their healthcare provider if they experience any signs or symptoms of bleeding.

Tumor Lysis Syndrome (TLS): Advise patients to contact their healthcare provider promptly to report any signs and symptoms of TLS.

Risk of Impaired Wound Healing: Advise patients that GAVRETO may impair wound healing. Advise patients that temporary interruption of GAVRETO is recommended prior to any elective surgery.

To review the full patient counseling information, please see the full Prescribing Information.

SELECT SAFETY INFORMATION

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.1% of patients treated with GAVRETO. Increased aspartate aminotransferase (AST) occurred in 69% of patients, including Grade 3/4 in 5% and increased alanine aminotransferase (ALT) occurred in 46% of patients, including Grade 3/4 in 6%. 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 initiating 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.

Please see additional Select Safety Information throughout, and click here to see the full Prescribing Information for GAVRETO.

GAVRETO™ pralsetinib 100mg capsules

GAVRETO dosing can be modified in response to adverse reactions[1]

Recommended dosage modifications for adverse reactions

Adverse reaction	Severity*	Dosage modification
ILD/Pneumonitis	Grade 1 or 2	Withhold GAVRETO until resolution. Resume by reducing the dose as shown in Table 1 of the GAVRETO full Prescribing Information. Permanently discontinue GAVRETO for recurrent ILD/pneumonitis.
	Grade 3 or 4	Permanently discontinue for confirmed ILD/pneumonitis.
Pneumonitis occurred in 10% of 438 patients who received GAVRETO at 400 mg once daily. Median time to onset was 12.1 weeks and median time to resolution was 8.4 weeks (range 3.6-12.1 weeks).[2]		
Hypertension	Grade 3	Withhold GAVRETO for Grade 3 hypertension that persists despite optimal antihypertensive therapy. Resume at a reduced dose when hypertension is controlled.
	Grade 4	Discontinue GAVRETO.
Hepatotoxicity	Grade 3 or Grade 4	Withhold GAVRETO and monitor AST/ALT once weekly until resolution to Grade 1 or baseline. Resume at reduced dose (Table 1). If hepatotoxicity recurs at Grade 3 or higher, discontinue GAVRETO.
Hemorrhagic Events	Grade 3 or Grade 4	Withhold GAVRETO until recovery to baseline or Grade 0 or 1. Discontinue GAVRETO for severe or life-threatening hemorrhagic events.
Other Adverse Reactions	Grade 3 or 4	Withhold GAVRETO until improvement to ≤ Grade 2. Resume at reduced dose (Table 1). Permanently discontinue for recurrent Grade 4 adverse reactions.

*Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

Recommended dose modification for coadministration[1]

Drug Interactions

- Strong CYP3A inhibitors: Avoid coadministration.
- Combined P-gp and Strong CYP3A inhibitors: Avoid coadministration. If coadministration cannot be avoided, reduce the dose of GAVRETO as shown in Table 3 of the Prescribing Information.
- Strong CYP3A inducers: Avoid coadministration. If coadministration cannot be avoided, increase the dose of GAVRETO as shown in Section 2.5 of the Prescribing Information.

Recommended dosage modifications for GAVRETO for coadministration with combined P-gp and strong CYP3A inhibitors

Current GAVRETO dosage	Recommended GAVRETO dosage
400 mg orally once daily	200 mg orally once daily
300 mg orally once daily	200 mg orally once daily
200 mg orally once daily	100 mg orally once daily

SELECT SAFETY INFORMATION

Grade ≥ 3 **hemorrhagic events** occurred in 2.5% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event. Permanently discontinue GAVRETO in patients with severe or life-threatening hemorrhage.

Tumor Lysis Syndrome (TLS): Cases of 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. Therefore, 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.

Please see additional Select Safety Information throughout, and click here to see the full Prescribing Information for GAVRETO.

GAVRETO™ pralsetinib 100mg capsules

Safety of GAVRETO was evaluated in 438 patients with RET-altered tumors, including RET+ mNSCLC (n=220) and RET-altered thyroid cancer (n=138), in ARROW[1]

Safety of GAVRETO in 438 patients with RET-altered tumors

- **The most common adverse reactions (≥25%) were constipation, hypertension, fatigue, musculoskeletal pain and diarrhea.**
- **The most common Grade 3-4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased phosphate, decreased calcium (corrected), decreased sodium, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), decreased platelets, and increased alkaline phosphatase.**
- **In 34 patients with RET-altered solid tumors, no large mean increase in QTc (>20 ms) was detected in the study.**

Safety of GAVRETO in 220 patients with RET+ mNSCLC[1]

15% of patients permanently discontinued GAVRETO due to any adverse reaction; **6.4%** discontinued due to adverse reactions considered treatment-related by the trial investigator[1,2]

Adverse reactions resulting in permanent discontinuation included pneumonitis (1.8%), pneumonia (1.8%), and sepsis (1%).

Serious adverse reactions occurred in 45% of patients who received GAVRETO. The most frequent serious adverse reaction (in ≥2% of patients) was pneumonia, pneumonitis, sepsis, urinary tract infection, and pyrexia. Fatal adverse reaction occurred in 5% of patients; fatal adverse reaction which occurred in > 1 patient included pneumonia (n=3) and sepsis (n=2).

36% | **of GAVRETO-treated patients had dose reductions due to adverse reactions.**

Adverse reactions requiring dosage reductions in ≥2% of patients included neutropenia, anemia, pneumonitis, neutrophil count decreased, fatigue, hypertension, pneumonia, and leukopenia.

60% | **of GAVRETO-treated patients had dose interruptions due to adverse reactions.**

Adverse reactions requiring dosage interruption in ≥2% of patients included neutropenia, pneumonitis, anemia, hypertension, pneumonia, pyrexia, increased aspartate aminotransferase (AST), increased blood creatine phosphokinase, fatigue, leukopenia, thrombocytopenia, vomiting, increased alanine aminotransferase (ALT), sepsis, and dyspnea.

mNSCLC=metastatic non–small cell lung cancer.

SELECT SAFETY INFORMATION

Based on findings from animal studies and its mechanism of action, GAVRETO can cause **fetal harm** when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the final dose. Advise women not to breastfeed during treatment with GAVRETO and for 1 week after the final dose.

Safety of GAVRETO in 138 patients with RET-altered thyroid cancer[1]

9% of patients permanently discontinued GAVRETO due to any adverse reaction; **3.6%** discontinued due to adverse reactions considered treatment-related by the trial investigator[1,2]

Adverse reactions resulting in permanent discontinuation which occurred in >1 patient included fatigue, pneumonia and anemia.

Serious adverse reactions occurred in 39% of patients who received GAVRETO. The most frequent serious adverse reactions (in ≥2% of patients) were pneumonia, pneumonitis, urinary tract infection, pyrexia, fatigue, diarrhea, dizziness, anemia, hyponatremia, and ascites. Fatal adverse reactions occurred in 2.2% of patients; fatal adverse reactions that occurred in > 1 patient included pneumonia (n=2).

44% | **Dose reductions due to adverse reactions in GAVRETO-treated patients.**

Adverse reactions requiring dosage reductions in ≥2% of patients included neutropenia, anemia, hypertension, increased blood creatine phosphokinase, decreased lymphocyte count, pneumonitis, fatigue and thrombocytopenia.

67% | **Dosage interruptions due to an adverse reaction in GAVRETO-treated patients.**

Adverse reactions requiring dosage interruption in ≥2% of patients included neutropenia, hypertension, diarrhea, fatigue, pneumonitis, anemia, increased blood creatine phosphokinase, pneumonia, urinary tract infection, musculoskeletal pain, vomiting, pyrexia, increased AST, dyspnea, hypocalcemia, cough, thrombocytopenia, abdominal pain, increased blood creatinine, dizziness, headache, decreased lymphocyte count, stomatitis, and syncope.

SELECT SAFETY INFORMATION

Common adverse reactions (≥25%) were constipation, hypertension, fatigue, musculoskeletal pain and diarrhea. **Common Grade 3/4 laboratory abnormalities (≥2%)** were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased phosphate, decreased calcium (corrected), decreased sodium, increased AST, increased ALT, decreased platelets and increased alkaline phosphatase.

Avoid coadministration of GAVRETO with **strong CYP3A inhibitors or combined P-gp** and **strong CYP3A inhibitors**. If coadministration cannot be avoided, reduce the GAVRETO dose. Avoid coadministration of GAVRETO with **strong CYP3A inducers**. If coadministration cannot be avoided, increase the GAVRETO dose.

Please see additional Select Safety Information throughout, and click here to see the full Prescribing Information for GAVRETO.

GAVRETO™ pralsetinib 100mg capsules

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A support program for your patients

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- Temporary treatment programs
- Reimbursement support

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Monday–Friday 8AM–8PM Eastern Time (ET)

References: 1. GAVRETO™ (pralsetinib). Prescribing Information. Blueprint Medicines Corporation; Cambridge, MA. December 2020. **2.** Data on file. Blueprint Medicines Corporation. Cambridge, MA 2020.

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