

GAVRETO- pralsetinib capsule

Genentech, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GAVRETO safely and effectively. See full prescribing information for GAVRETO.

GAVRETO® (pralsetinib) capsules, for oral use
Initial U.S. Approval: 2020

RECENT MAJOR CHANGES

Indications and Usage, Metastatic <i>RET</i> Fusion-Positive Non-Small Cell Lung Cancer – Accelerated Approval text removed (1.1)	(8/2023)
Indications and Usage, <i>RET</i> -Mutant Medullary Thyroid Cancer – Indication Removed (1.2)	(7/2023)
Dosage and Administration (2.1)	(7/2023)
Dosage and Administration, Dose Modification for Use with CYP3A and/or P-glycoprotein (P-gp) Inhibitors (2.4)	(6/2023)
Dosage and Administration, Dose Modification for Use with CYP3A Inducers (2.5)	(6/2023)

INDICATIONS AND USAGE

GAVRETO is a kinase inhibitor indicated for treatment of:

- Adult patients with metastatic rearranged during transfection (*RET*) fusion-positive non-small cell lung cancer as detected by an FDA approved test (NSCLC). (1.1)
- Adult 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).

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). (1.2)

DOSAGE AND ADMINISTRATION

Select patients for treatment with GAVRETO based on the presence of a *RET* gene fusion. (2.1, 14)
The recommended dosage in adults and pediatric patients 12 years and older is 400 mg orally once daily on an empty stomach (no food intake for at least 2 hours before and at least 1 hour after taking GAVRETO). (2.2)

DOSAGE FORMS AND STRENGTHS

Capsules: 100 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- **Interstitial Lung Disease (ILD)/Pneumonitis:** Withhold GAVRETO for Grade 1 or 2 reactions until resolution and then resume at a reduced dose. Permanently discontinue for recurrent ILD/pneumonitis. Permanently discontinue for Grade 3 or 4 reactions. (2.3, 5.1)
- **Hypertension:** Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure (BP) prior to initiating GAVRETO. Monitor BP after 1 week, at least monthly thereafter and as clinically indicated. Withhold, reduce dose, or permanently discontinue GAVRETO based on severity. (2.3, 5.2)
- **Hepatotoxicity:** Monitor ALT and AST 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. (2.3, 5.3)
- **Hemorrhagic Events:** Permanently discontinue GAVRETO in patients with severe or life-threatening hemorrhage. (2.3, 5.4)
- **Tumor Lysis Syndrome:** Closely monitor patients at risk and treat as clinically indicated. (2.3, 5.5)
- **Risk of Impaired 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. (5.6)

- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective non-hormonal contraception. (5.7, 8.1, 8.3)

ADVERSE REACTIONS

- The most common adverse reactions ($\geq 25\%$) were musculoskeletal pain, constipation, hypertension, diarrhea, fatigue, edema, pyrexia and cough.
- The most common Grade 3-4 laboratory abnormalities ($\geq 2\%$) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased phosphate, decreased leukocytes, decreased sodium, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), decreased calcium (corrected), decreased platelets, increased alkaline phosphatase, increased potassium, decreased potassium and increased bilirubin. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Strong or moderate CYP3A inhibitors and/or P-gp inhibitors:** Avoid coadministration. If coadministration cannot be avoided, reduce the dose of GAVRETO. (2.4, 7.1, 12.3)
- **Strong or moderate CYP3A inducers:** Avoid coadministration. If coadministration cannot be avoided, increase the dose of GAVRETO. (2.5, 7.1, 12.3)

USE IN SPECIFIC POPULATIONS

- **Lactation:** Advise not to breastfeed. (8.2)
- **Pediatric Use:** Monitor open growth plates in adolescent patients. Consider interrupting or discontinuing GAVRETO if abnormalities occur. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 8/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Metastatic *RET* Fusion-Positive Non-Small Cell Lung Cancer
- 1.2 *RET* Fusion-Positive Thyroid Cancer

2 DOSAGE AND ADMINISTRATION

- 2.1 Patient Selection
- 2.2 Recommended Dosage
- 2.3 Dosage Modifications for Adverse Reactions
- 2.4 Dose Modification for Use with CYP3A and/or P-glycoprotein (P-gp) Inhibitors
- 2.5 Dose Modification for Use with CYP3A Inducers

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Interstitial Lung Disease/Pneumonitis
- 5.2 Hypertension
- 5.3 Hepatotoxicity
- 5.4 Hemorrhagic Events
- 5.5 Tumor Lysis Syndrome
- 5.6 Risk of Impaired Wound Healing
- 5.7 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on GAVRETO

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Metastatic *RET* Fusion-Positive Non-Small Cell Lung Cancer

14.2 *RET* Fusion-Positive Thyroid Cancer

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Metastatic *RET* Fusion-Positive Non-Small Cell Lung Cancer

GAVRETO is indicated for the treatment of adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.

1.2 *RET* Fusion-Positive Thyroid Cancer

GAVRETO is indicated for the treatment of adult 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).

This indication is approved under accelerated approval based on overall response rate and duration of response [see *Clinical Studies (14.2)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment with GAVRETO based on the presence of a *RET* gene fusion (NSCLC or thyroid cancer) [see *Clinical Studies (14)*].

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) is not currently available.

2.2 Recommended Dosage

The recommended dosage of GAVRETO is 400 mg orally once daily on an empty stomach (no food intake for at least 2 hours before and at least 1 hour after taking GAVRETO) [see *Clinical Pharmacology (12.3)*]. 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.

Do not take an additional dose if vomiting occurs after GAVRETO but continue with the next dose as scheduled.

2.3 Dosage Modifications for Adverse Reactions

The recommended dose reductions and dosage modifications for adverse reactions are provided in Table 1 and Table 2.

Table 1: Recommended Dose Reductions for GAVRETO for Adverse Reactions

Dose Reduction	Recommended Dosage
First	300 mg once daily
Second	200 mg once daily
Third	100 mg once daily

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

The recommended dosage modifications for adverse reactions are provided in Table 2.

Table 2: Recommended Dosage Modifications for GAVRETO for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
	Grade 1 or 2	Withhold GAVRETO until resolution. Resume by reducing the dose as shown in Table 1. Permanently

ILD/Pneumonitis <i>[see Warnings and Precautions (5.1)]</i>		Permanently discontinue GAVRETO for recurrent ILD/pneumonitis.
	Grade 3 or 4	Permanently discontinue for confirmed ILD/pneumonitis.
Hypertension <i>[see Warnings and Precautions (5.2)]</i>	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 <i>[see Warnings and Precautions (5.3)]</i>	Grade 3 or 4	Withhold GAVRETO and monitor AST/ALT once weekly until resolution to Grade 1 or baseline. Resume at reduced dose (Table 1). For recurrent events at Grade 3 or higher, discontinue GAVRETO.
Hemorrhagic Events <i>[see Warnings and Precautions (5.4)]</i>	Grade 3 or 4	Withhold GAVRETO until recovery to baseline or Grade 0 or 1. Discontinue GAVRETO for severe or life-threatening hemorrhagic events.
Other Adverse Reactions <i>[see Adverse Reactions (6.1)]</i>	Grade 3 or 4	Withhold GAVRETO until improvement to \leq 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

2.4 Dose Modification for Use with CYP3A and/or P-glycoprotein (P-gp) Inhibitors

Avoid coadministration of GAVRETO with any of the following:

- Strong CYP3A inhibitors
- Moderate CYP3A inhibitors
- P-gp inhibitors
- Combined P-gp and strong CYP3A inhibitors
- Combined P-gp and moderate CYP3A inhibitors

If coadministration with any of the above inhibitors cannot be avoided, reduce the current dose of GAVRETO as recommended in Table 3. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume GAVRETO at the dose taken prior to initiating the inhibitor [see *Drug Interactions (7.1)*, *Clinical Pharmacology (12.3)*].

Table 3: Recommended Dosage Modifications for GAVRETO for Coadministration with CYP3A and/or P-gp Inhibitors

Current GAVRETO Dosage	Recommended GAVRETO Dosage when Coadministered with:	
	Combined P-gp and Strong CYP3A Inhibitors	<ul style="list-style-type: none"> • Strong CYP3A Inhibitors; • Moderate CYP3A Inhibitors; • P-gp Inhibitors; • Combined P-gp and Moderate CYP3A Inhibitors
400 mg orally once daily	200 mg orally once daily	300 mg orally once daily
300 mg orally once daily	200 mg orally once daily	200 mg orally once daily
200 mg orally once daily	100 mg orally once daily	100 mg orally once daily

2.5 Dose Modification for Use with CYP3A Inducers

Avoid coadministration of GAVRETO with any of the following:

- Strong CYP3A inducers
- Moderate CYP3A inducers

If coadministration with any of the above inducers cannot be avoided, increase the starting dose of GAVRETO as recommended in Table 4 starting on Day 7 of coadministration of GAVRETO with the inducer. After the inducer has been discontinued

for at least 14 days, resume GAVRETO at the dose taken prior to initiating the inducer [see Drug Interactions (7.1), Clinical Pharmacology (12.3)].

Table 4: Recommended Dosage Modifications for GAVRETO for Coadministration with CYP3A Inducers

Current GAVRETO Dosage	Recommended GAVRETO Dosage when Coadministered with:	
	Strong CYP3A Inducers	Moderate CYP3A Inducers
400 mg orally once daily	800 mg orally once daily	600 mg orally once daily
300 mg orally once daily	600 mg orally once daily	500 mg orally once daily
200 mg orally once daily	400 mg orally once daily	300 mg orally once daily

3 DOSAGE FORMS AND STRENGTHS

Capsules: 100 mg, light blue, opaque, hard hydroxypropyl methylcellulose (HPMC) capsule printed with "BLU-667" on the capsule shell body and "100 mg" on the capsule shell cap.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, and fatal interstitial lung disease (ILD) / pneumonitis can occur in patients treated with GAVRETO. Pneumonitis occurred in 12% of patients who received GAVRETO, including 3.3% with Grade 3-4, and 0.2% 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 which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD [see Dosage and Administration (2.3)].

5.2 Hypertension

Hypertension occurred in 35% of patients, including Grade 3 hypertension in 18% of patients [see Adverse Reactions (6.1)]. Overall, 8% had their dose interrupted and 4.8% 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 [see *Dosage and Administration (2.3)*].

5.3 Hepatotoxicity

Serious hepatic adverse reactions occurred in 1.5% of patients treated with GAVRETO. Increased AST occurred in 49% of patients, including Grade 3 or 4 in 7% and increased ALT occurred in 37% of patients, including Grade 3 or 4 in 4.8% [see *Adverse Reactions (6.1)*]. The median time to first onset for increased AST was 15 days (range: 5 days to 2.5 years) and for increased ALT was 24 days (range: 7 days to 3.7 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 [see *Dosage and Administration (2.3)*].

5.4 Hemorrhagic Events

Serious, including fatal, hemorrhagic events can occur with GAVRETO. Grade ≥ 3 hemorrhagic events occurred in 4.1% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event.

Permanently discontinue GAVRETO in patients with severe or life-threatening hemorrhage [see *Dosage and Administration (2.3)*].

5.5 Tumor Lysis Syndrome

Cases of tumor lysis syndrome (TLS) have been reported in patients with medullary thyroid carcinoma receiving GAVRETO [see *Adverse Reactions (6.1)*]. 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.

5.6 Risk of Impaired Wound Healing

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.

5.7 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryoletality at maternal exposures below the human exposure at the clinical dose of 400 mg once daily.

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 last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the last dose [see *Use in Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Interstitial Lung Disease/Pneumonitis [see *Warnings and Precautions (5.1)*]
- Hypertension [see *Warnings and Precautions (5.2)*]
- Hepatotoxicity [see *Warnings and Precautions (5.3)*]
- Hemorrhagic Events [see *Warnings and Precautions (5.4)*]
- Tumor Lysis Syndrome [see *Warnings and Precautions (5.5)*]
- Risk of Impaired Wound Healing [see *Warnings and Precautions (5.6)*]
- Embryo-Fetal Toxicity [see *Warnings and Precautions (5.7)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population in the WARNINGS AND PRECAUTIONS reflect exposure to GAVRETO as a single agent at 400 mg orally once daily in 540 patients in ARROW [see *Clinical Studies (14)*]. Among 540 patients who received GAVRETO, 71% were exposed for 6 months or longer and 57% were exposed for greater than one year. The most common adverse reactions ($\geq 25\%$) were musculoskeletal pain, constipation, hypertension, diarrhea, fatigue, edema, pyrexia, and cough. The most common Grade 3-4 laboratory abnormalities ($\geq 2\%$) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased phosphate, decreased leukocytes, decreased sodium, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), decreased calcium (corrected), decreased platelets, increased alkaline phosphatase, increased potassium, decreased potassium and increased bilirubin.

RET Fusion-Positive Non-Small Cell Lung Cancer

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 281 patients with metastatic rearranged during transfection (*RET* fusion-positive) non-small cell lung cancer (NSCLC) in ARROW [see *Clinical Studies (14.1)*]. Among the 281 patients who received GAVRETO, 72% were exposed for 6 months or longer and 56% were exposed for ≥ 1 year.

The median age was 60 years (range: 26 to 87 years); 54% were female, 46% were White, 46% were Asian, and 4% were Hispanic/Latino.

Serious adverse reactions occurred in 65% of patients who received GAVRETO. The most frequent serious adverse reactions (in $\geq 2\%$ of patients) were pneumonia, anemia, pneumonitis, pyrexia, sepsis, urinary tract infection, coronavirus infection, pleural effusion, dyspnea, musculoskeletal pain, pulmonary embolism, and seizure. Fatal adverse reactions occurred in 7% of patients; fatal adverse reactions which occurred in

> 1 patient included pneumonia (n = 8), sepsis (n=3) and COVID (n=3).

Permanent discontinuation due to an adverse reaction occurred in 20% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation which occurred in $\geq 2\%$ of patients included pneumonitis (3.2%), and pneumonia (2.8%).

Dosage interruptions due to an adverse reaction occurred in 73% of patients who received GAVRETO. Adverse reactions requiring dosage interruption in $\geq 2\%$ of patients included anemia, pneumonia, pneumonitis, neutropenia, hypertension, increased blood creatine phosphokinase, fatigue, pyrexia, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), coronavirus infection, diarrhea, hypophosphatemia, musculoskeletal pain, thrombocytopenia, dyspnea, hemorrhage, leukopenia, lymphopenia, edema, sepsis, and vomiting.

Dose reductions due to adverse reactions occurred in 51% of patients who received GAVRETO. Adverse reactions requiring dosage reductions in $\geq 2\%$ of patients included anemia, neutropenia, pneumonitis, increased blood creatine phosphokinase, leukopenia, hypertension, fatigue, pneumonia, and lymphopenia.

Table 5 summarizes the adverse reactions in patients with NSCLC in ARROW.

Table 5: Adverse Reactions ($\geq 15\%$) in RET Fusion-Positive NSCLC Patients Who Received GAVRETO in ARROW

Adverse reaction	GAVRETO N = 281	
	Grades 1 - 4 (%)	Grades 3 or 4 (%)
Gastrointestinal disorders		
Constipation	45	0.7
Diarrhea	30	2.5
Nausea	19	0
Dry mouth	17	0
General Disorders and Administration Site Conditions		
Edema*	44	0
Fatigue†	42	2.5
Pyrexia	29	0.7
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain‡	44	2.5
Increased Blood Creatine Phosphokinase	19	9
Vascular		
Hypertension§	38	18
Respiratory, thoracic and mediastinal disorders		
Cough¶	36	0.4
Dyspnea	21	2.1
Infection and Infestations		
Pneumonia#	24	13

Urinary tract infection	16	3.6
Metabolism and Nutrition Disorders		
Decreased appetite	18	1.1
Nervous system disorders		
Taste disorder ^p	17	0
Headache ^β	15	1.1
Skin and subcutaneous tissue disorders		
Rash ^à	17	0

* Includes the preferred terms: Edema, Swelling face, Peripheral swelling, Generalized oedema, Edema peripheral, Face edema, Periorbital edema, Eyelid edema, Swelling, Localized edema

† Includes the preferred terms: Fatigue, Asthenia

‡ Includes the preferred terms: Myalgia, Arthralgia, Pain in extremity, Neck pain, Musculoskeletal pain, Back pain, Musculoskeletal chest pain, Bone pain, Musculoskeletal stiffness

§ Includes the preferred terms: hypertension, blood pressure increased

¶ Includes the preferred terms: Cough, Productive Cough, upper-airway cough syndrome

Includes the preferred terms: Pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia cytomegaloviral, Atypical pneumonia, Lung infection, Pneumonia bacterial, Pneumonia haemophilus, Pneumonia influenzal, Pneumonia streptococcal, Pneumonia viral, Pneumonia pseudomonal

p Includes the preferred terms: Dysgeusia, Ageusia

β Includes the preferred terms: Headache, Tension Headache

à Includes the preferred terms: Rash, Rash maculo-papular, Dermatitis acneiform, Erythema, Rash generalized, Rash papular, Rash macular, Rash erythematous

Clinically relevant adverse reactions occurring in < 15% of patients included pneumonitis (14%), vomiting (14%), abdominal pain (14%), and stomatitis (6%).

Table 6 summarizes the laboratory abnormalities in ARROW.

Table 6: Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in RET Fusion-Positive NSCLC Patients Who Received GAVRETO in ARROW

Laboratory Abnormality	GAVRETO N=281	
	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry		
Increased AST	80	3.2
Increased ALT	58	3.9
Decreased albumin	52	0
Decreased calcium (corrected)	50	1.8
Decreased phosphate	50	17
Increased creatinine	45	1.4
Increased alkaline phosphatase	43	2.5

Decreased sodium	42	10
Decreased Potassium	27	4.6
Increased Potassium	27	1.8
Decreased Magnesium	25	0
Increased Bilirubin	20	1.8
Hematology		
Decreased leukocytes	79	11
Decreased hemoglobin	78	18
Decreased lymphocytes	73	32
Decreased neutrophils	70	21
Decreased platelets	33	5

Clinically relevant laboratory abnormalities occurring in < 20% of patients who received GAVRETO included increased magnesium (14%).

RET-altered Thyroid Cancer

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 138 patients with *RET*-altered thyroid cancer (including 19 patients with *RET* fusion-positive thyroid cancer) in ARROW [see *Clinical Studies (14.2)*]. Among the 138 patients who received GAVRETO, 68% were exposed for 6 months or longer, and 40% were exposed for greater than one year.

The median age was 59 years (range: 18 to 83 years); 36% were female, 74% were White, 17% were Asian, and 6% were Hispanic/Latino.

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

Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation which occurred in > 1 patient included fatigue, pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 67% of patients who received GAVRETO. Adverse reactions requiring dosage interruption in $\geq 2\%$ 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.

Dose reductions due to adverse reactions occurred in 44% of patients who received GAVRETO. Adverse reactions requiring dosage reductions in $\geq 2\%$ of patients included neutropenia, anemia, hypertension, increased blood creatine phosphokinase, decreased lymphocyte count, pneumonitis, fatigue and thrombocytopenia.

Table 7 summarizes the adverse reactions occurring in *RET*-altered Thyroid Cancer Patients in ARROW.

Table 7: Adverse Reactions (≥ 15%) in RET-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW

Adverse Reactions	GAVRETO N=138	
	Grades 1-4 (%)	Grades 3-4 (%)
Musculoskeletal		
Musculoskeletal Pain*	42	0.7†
Gastrointestinal		
Constipation	41	0.7†
Diarrhea‡	34	5†
Abdominal Pain§	17	0.7†
Dry mouth	17	0
Stomatitis¶	17	0.7†
Nausea	17	0.7†
Vascular		
Hypertension	40	21†
General		
Fatigue#	38	6†
Edema ^p	29	0
Pyrexia	22	2.2†
Respiratory		
Cough ^β	27	1.4†
Dyspnea ^à	22	2.2†
Nervous System		
Headache ^è	24	0
Peripheral Neuropathy ^ð	20	0
Dizziness ^ø	19	0.7†
Dysgeusia ^ý	17	0
Skin and Subcutaneous		
Rash [£]	24	0
Metabolism and Nutrition		
Decreased Appetite	15	0

* Musculoskeletal Pain includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain

† Only includes a Grade 3 adverse reaction

‡ Diarrhea includes colitis, diarrhea

§ Abdominal Pain includes abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness, epigastric discomfort

¶ Stomatitis includes mucosal inflammation, stomatitis, tongue ulceration

Fatigue includes asthenia, fatigue

^p Edema includes eyelid edema, face edema, edema, edema peripheral, periorbital edema

^β Cough includes cough, productive cough, upper-airway cough syndrome

^à Dyspnea includes dyspnea, dyspnea exertional

^è Headache includes headache, migraine

- ð Peripheral neuropathy includes dysaesthesia, hyperaesthesia, hypoaesthesia, neuralgia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, polyneuropathy
- ø Dizziness includes dizziness, dizziness postural, vertigo
- ý Dysgeusia includes ageusia, dysgeusia
- £ Rash includes dermatitis, dermatitis acneiform, eczema, palmar-plantar, erythroderma syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular

Clinically relevant adverse reactions in < 15% of patients who received GAVRETO included tumor lysis syndrome and increased creatine phosphokinase.

Table 8 summarizes the laboratory abnormalities occurring in *RET*-altered Thyroid Cancer Patients in ARROW.

Table 8: Select Laboratory Abnormalities ($\geq 20\%$) Worsening from Baseline in *RET*-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW

Laboratory Abnormality	GAVRETO N=138	
	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry		
Decreased calcium (corrected)	70	9
Increased AST	69	4.3
Increased ALT	43	3.6
Increased creatinine	41	0
Decreased albumin	41	1.5
Decreased sodium	28	2.2
Decreased phosphate	28	8
Decreased magnesium	27	0.7
Increased potassium	26	1.4
Increased bilirubin	24	1.4
Increased alkaline phosphatase	22	1.4
Hematology		
Decreased lymphocytes	67	27
Decreased hemoglobin	63	13
Decreased neutrophils	59	16
Decreased platelets	31	2.9

Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 135 to 138 patients.

Clinically relevant laboratory abnormalities in patients who received GAVRETO included increased phosphate (40%).

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on GAVRETO

Strong or Moderate CYP3A and/or P-gp Inhibitors

Concomitant use with a strong or moderate CYP3A inhibitor and/or a P-gp inhibitor increases pralsetinib exposure [*Clinical Pharmacology (12.3)*], which may increase the risk of adverse reactions related to GAVRETO. Avoid coadministration of GAVRETO with a strong or moderate CYP3A and/or P-gp inhibitor. If coadministration with any of the above inhibitors cannot be avoided, reduce the GAVRETO dose [*see Dosage and Administration (2.4)*].

Strong or moderate CYP3A Inducers

Concomitant use with a strong CYP3A inducer decreases pralsetinib exposure [*see Clinical Pharmacology (12.3)*], which may decrease efficacy of GAVRETO. Avoid concomitant use of GAVRETO with strong or moderate CYP3A inducers. If coadministration of GAVRETO with strong or moderate CYP3A inducers cannot be avoided, increase the GAVRETO dose [*see Dosage and Administration (2.5)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman [*see Clinical Pharmacology (12.1)*]. There are no available data on GAVRETO use in pregnant women to inform drug-associated risk. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryoletality at maternal exposures below the human exposure at the clinical dose of 400 mg once daily (*see Data*). Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study, once daily oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in 100% post-implantation loss at dose levels ≥ 20 mg/kg (approximately 1.8 times the human exposure based on area under the curve [AUC] at the clinical dose of 400 mg). Post-implantation loss also occurred at the 10 mg/kg dose level (approximately 0.6 times the human exposure based on AUC at the clinical dose of 400 mg). Once daily oral administration of pralsetinib at dose levels ≥ 5 mg/kg (approximately 0.2 times the human AUC at the clinical dose of 400 mg) resulted in an increase in visceral malformations and variations (absent or small kidney and ureter, absent uterine horn, malpositioned kidney or testis, retroesophageal aortic arch) and skeletal malformations and variations (vertebral and rib anomalies and reduced ossification).

8.2 Lactation

Risk Summary

There are no data on the presence of pralsetinib or its metabolites in human milk or their effects on either the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with GAVRETO and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

Based on animal data, GAVRETO can cause embryoletality and malformations at doses resulting in exposures below the human exposure at the clinical dose of 400 mg daily [see *Use in Specific Populations (8.1)*].

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating GAVRETO [see *Use in Specific Populations (8.1)*].

Contraception

GAVRETO can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*].

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the last dose. GAVRETO may render hormonal contraceptives ineffective.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the last dose.

Infertility

Based on histopathological findings in the reproductive tissues of male and female rats and a dedicated fertility study in which animals of both sexes were treated and mated to each other, GAVRETO may impair fertility [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of GAVRETO have been established in pediatric patients aged 12 years and older for *RET* fusion-positive thyroid cancer. Use of GAVRETO in this age group is supported by evidence from an adequate and well-controlled study of GAVRETO in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the pharmacokinetics of pralsetinib, that the exposure of pralsetinib is expected to be similar between adults and pediatric patients age 12 years and older, and that the course of *RET* fusion-positive thyroid cancer is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients [see *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14.2)*].

The safety and effectiveness of GAVRETO have not been established in pediatric patients with *RET* fusion-positive NSCLC or in pediatric patients younger than 12 years old with

RET fusion-positive thyroid cancer.

Animal Toxicity Data

In a 4-week repeat-dose toxicology study in non-human primates, physal dysplasia in the femur occurred at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. In rats there were findings of increased physal thickness in the femur and sternum as well as tooth (incisor) abnormalities (fractures, dentin matrix alteration, ameloblast/odontoblast degeneration, necrosis) in both 4- and 13-week studies at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. Recovery was not assessed in the 13-week toxicology study, but increased physal thickness in the femur and incisor degeneration did not show evidence of complete recovery in the 28-day rat study.

Monitor growth plates in adolescent patients with open growth plates. Consider interrupting or discontinuing therapy based on the severity of any growth plate abnormalities and based on an individual risk-benefit assessment.

8.5 Geriatric Use

Of the 540 patients in ARROW who received the recommended dose of GAVRETO at 400 mg once daily, 31% were 65 years or and over, while 7% were 75 years and over.

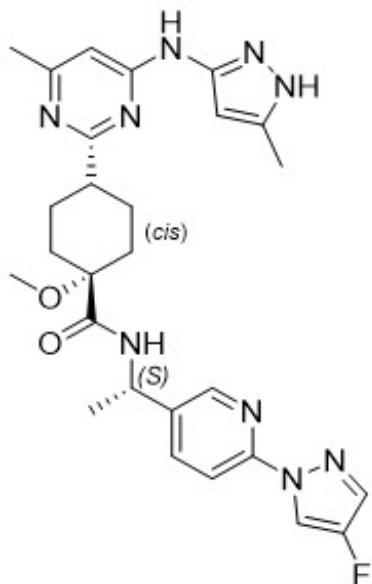
No overall differences in pharmacokinetics (PK), safety or effectiveness were observed between patients aged 65 years or older and younger patients.

8.6 Hepatic Impairment

GAVRETO has not been studied in patients with moderate hepatic impairment (total bilirubin > 1.5 to 3.0 × upper limit of normal [ULN] and any aspartate aminotransferase [AST]) or severe hepatic impairment (total bilirubin > 3.0 × ULN and any AST). No dose adjustment is required for patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 times ULN and any AST) [see *Clinical Pharmacology* (12.3)].

11 DESCRIPTION

Pralsetinib is an oral receptor tyrosine kinase inhibitor. The chemical name for pralsetinib is (*cis*)-*N*-((*S*)-1-(6-(4-fluoro-1*H*-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-yl)cyclohexanecarboxamide. The molecular formula for pralsetinib is C₂₇H₃₂FN₉O₂, and the molecular weight is 533.61 g/mol. Pralsetinib has the following structure:



The solubility of pralsetinib in aqueous media decreases over the range pH 1.99 to pH 7.64 from 0.880 mg/mL to < 0.001 mg/mL, indicating a decrease in solubility with increasing pH.

GAVRETO (pralsetinib) is supplied for oral use as immediate release hydroxypropyl methylcellulose (HPMC) hard capsules containing 100 mg pralsetinib. The capsules also contain inactive ingredients:

citric acid, hydroxypropyl methylcellulose (HPMC), magnesium stearate, microcrystalline cellulose (MCC), pregelatinized starch and sodium bicarbonate. The capsule shell consists of FD&C Blue #1 (Brilliant Blue FCF), hypromellose and titanium dioxide. The white printing ink contains butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pralsetinib is a kinase inhibitor of wild-type *RET* and oncogenic *RET* fusions (CCDC6-*RET*) and mutations (*RET* V804L, *RET* V804M and *RET* M918T) with half maximal inhibitory concentrations (IC_{50s}) less than 0.5 nM. In purified enzyme assays, pralsetinib inhibited DDR1, TRKC, FLT3, JAK1-2, TRKA, VEGFR2, PDGFRB, and FGFR1 at higher concentrations that were still clinically achievable at C_{max} . In cellular assays, pralsetinib inhibited *RET* at approximately 14-, 40-, and 12-fold lower concentrations than VEGFR2, FGFR2, and JAK2, respectively.

Certain *RET* fusion proteins and activating point mutations can drive tumorigenic potential through hyperactivation of downstream signaling pathways leading to uncontrolled cell proliferation. Pralsetinib exhibited anti-tumor activity in cultured cells and animal tumor implantation models harboring oncogenic *RET* fusions or mutations including KIF5B-*RET*, CCDC6-*RET*, *RET* M918T, *RET* C634W, *RET* V804E, *RET* V804L and *RET* V804M. In addition, pralsetinib prolonged survival in mice implanted intracranially with tumor models expressing KIF5B-*RET* or CCDC6-*RET*.

12.2 Pharmacodynamics

Pralsetinib exposure-response relationships and the time course of pharmacodynamics response have not been fully characterized.

Cardiac Electrophysiology

The QT interval prolongation potential of pralsetinib was assessed in 34 patients with *RET*-altered solid tumors administered GAVRETO at the recommended dosage. No large mean increase in QTc (> 20 ms) was detected in the study.

12.3 Pharmacokinetics

At 400 mg GAVRETO once daily under fasting conditions, the steady state geometric mean [% coefficient of variation (CV%)] of maximum observed plasma concentration (C_{max}) and area under the concentration-time curve (AUC_{0-24h}) of pralsetinib was 2470 (55.1%) ng/mL and 36700 (66.3%) h•ng/mL, respectively. Pralsetinib C_{max} and AUC increased inconsistently over the dose range of 60 mg to 600 mg once daily (0.15 to 1.5 times the recommended dose). Pralsetinib plasma concentrations reached steady state by 3 to 5 days. The mean accumulation ratio was approximately 2-fold after once-daily repeated oral administration.

Absorption

The median time to peak concentration (T_{max}) ranged from 2 to 4 hours following single doses of pralsetinib 60 mg to 600 mg.

Food Effect

Following administration of a single dose of 200 mg GAVRETO with a high-fat meal, (approximately 800 to 1000 calories with 50 to 60% of calories from fat), the mean (90% CI) C_{max} of pralsetinib was increased by 104% (65%, 153%), the mean (90% CI) AUC_{0-INF} was increased by 122% (96%, 152%), and the median T_{max} was delayed from 4 to 8.5 hours, compared to the fasted state.

Distribution

The mean (CV%) apparent volume of distribution (V_d/F) of pralsetinib is 303 L (68%). Protein binding of pralsetinib is 97.1% and is independent of concentration. The blood-to-plasma ratio is 0.6 to 0.7.

Elimination

The mean (\pm standard deviation) plasma elimination half-life ($T_{1/2}$) of pralsetinib is 15.7 hours (9.8) following single doses and 20 hours (11.7) following multiple doses of pralsetinib. The mean (CV%) apparent oral clearance (CL/F) of pralsetinib is 10.9 L/h (66%) at steady state.

Metabolism

Pralsetinib is primarily metabolized by CYP3A4 and to a lesser extent by CYP2D6 and CYP1A2, *in vitro*. Following a single oral dose of 310 mg of radiolabeled pralsetinib to healthy subjects, pralsetinib metabolites from oxidation and glucuronidation were detected as 5% or less.

Excretion

Approximately 73% (66% as unchanged) of the total administered radioactive dose [¹⁴C] pralsetinib was recovered in feces and 6% (4.8% as unchanged) was recovered in urine.

Specific Populations

No clinically significant differences in the PK of pralsetinib were observed based on age (19 to 87 years), sex, race (370 White, 22 Black, or 61 Asian), and body weight (32.1 to 128 kg). Mild and moderate renal impairment (CL_{cr} 30 - 89 mL/min) had no effect on the exposure of pralsetinib. Pralsetinib has not been studied in patients with severe renal impairment (CL_{cr} < 15 mL/min).

Patients with Hepatic Impairment

Mild hepatic impairment (total bilirubin ≤ 1.0 × ULN and AST > ULN, or total bilirubin > 1.0 to 1.5 × ULN and any AST) had no effect on the PK of pralsetinib. Pralsetinib has not been studied in patients with moderate (total bilirubin > 1.5 to 3.0 × ULN and any AST) or severe (total bilirubin > 3.0 ULN and any AST) hepatic impairment.

Drug Interaction Studies

Clinical Studies and Model-Informed Approach

CYP3A Inhibitors: Coadministration of multiple doses of CYP3A inhibitors increases pralsetinib C_{max} and AUC.

Table 9: Observed or Predicted Increase in Pralsetinib Exposure after Co-administration of CYP3A inhibitors

Type of inhibitor	Co-administered CYP3A Inhibitor	Increase in pralsetinib C _{max}	Increase in pralsetinib AUC
<i>Observed</i>			
P-gp and Strong CYP3A Inhibitor	Itraconazole (200 mg twice daily on Day 1, followed by 200 mg once daily)	84%	251%
<i>Predicted</i>			
Strong CYP3A Inhibitors	Voriconazole (400 mg twice daily on Day 1, followed by 200 mg twice daily)	20%	122%
Combined P-gp and Moderate CYP3A Inhibitors	Verapamil (80 mg three times daily)	60%	108%
Moderate CYP3A Inhibitors	Fluconazole (400 mg once daily)	15%	71%

P-gp Inhibitors: Coadministration of cyclosporine (single 600 mg dose) with a single 200 mg dose of pralsetinib in healthy subjects increased pralsetinib AUC_{0-inf} by 81% and C_{max} by 48%, relative to a 200 mg dose of pralsetinib administered alone

Strong CYP3A Inducers: Coadministration of rifampin 600 mg once daily with a single GAVRETO 400 mg dose decreased pralsetinib AUC_{0-inf} by 68% and C_{max} by 30%.

Moderate CYP3A Inducers: Coadministration of multiple doses of efavirenz (600 mg once daily) is predicted to decrease the pralsetinib AUC by 45% and C_{max} by 18%.

Mild CYP3A Inducers: No clinically significant differences in the PK of pralsetinib were identified when GAVRETO was coadministered with mild CYP3A inducers.

Acid-Reducing Agents: No clinically significant differences in the PK of pralsetinib were observed when GAVRETO was coadministered with gastric acid reducing agents.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Pralsetinib is a time-dependent inhibitor of CYP3A4/5 and an inhibitor of CYP2C8, CYP2C9, and CYP3A4/5, but not an inhibitor of CYP1A2, CYP2B6, CYP2C19 or CYP2D6 at clinically relevant concentrations.

Pralsetinib is an inducer of CYP2C8, CYP2C9, and CYP3A4/5, but not an inducer of CYP1A2, CYP2B6, or CYP2C19 at clinically relevant concentrations.

Transporter Systems: Pralsetinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but not a substrate of bile salt efflux pump (BSEP), organic cation transporter [OCT]1, OCT2, organic anion transporting polypeptide [OATP]1B1, OATP1B3, multidrug and toxin extrusion [MATE]1, MATE2-K, organic anion transporter [OAT]1, or OAT3.

Pralsetinib is an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1, MATE2-K, and BSEP, but not an inhibitor of OCT1, OCT2, and OAT1A3 at clinically relevant concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with pralsetinib have not been conducted. Pralsetinib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay with or without metabolic activation and was not clastogenic in either an in vitro micronucleus assay in TK6 cells or an in vivo bone marrow micronucleus assay in rats.

In a dedicated fertility and early embryonic development study conducted in treated male rats mated to treated female rats, although pralsetinib did not have clear effects on male or female mating performance or ability to become pregnant, at the 20 mg/kg dose level (approximately 2.9 times the human exposure (AUC) at the clinical dose of 400 mg based on toxicokinetic data from the 13-week rat toxicology study) 82% of female rats had totally resorbed litters, with 92% post-implantation loss (early resorptions); post-implantation loss occurred at doses as low as 5 mg/kg (approximately 0.35 times the human exposure (AUC) at the clinical dose of 400 mg based on toxicokinetic data from the 13-week rat toxicology study). In a separate fertility and early embryonic development study in which male rats administered 20 mg/kg pralsetinib were mated to untreated female rats, there were no clear pralsetinib-related effects on intrauterine survival of embryos or on male reproductive performance at a dose approximately 1.7 times the human exposure (AUC) at the clinical dose of 400 mg. In a 13-week repeat-dose toxicology study, male rats exhibited histopathological evidence of tubular degeneration/atrophy in the testis with secondary cellular debris and reduced sperm in the lumen of the epididymis, which correlated with lower mean testis and epididymis

weights and gross observations of soft and small testis. Female rats exhibited degeneration of the corpus luteum in the ovary. For both sexes, these effects were observed at pralsetinib doses ≥ 10 mg/kg/day, approximately 1 times the human exposure based on AUC at the clinical dose of 400 mg.

13.2 Animal Toxicology and/or Pharmacology

In 28-day rat and monkey toxicology studies, once daily oral administration of pralsetinib resulted in histologic necrosis and hemorrhage in the heart of preterm decedents at exposures ≥ 1.3 times and ≥ 3.1 times, respectively, the human exposure based on AUC at the clinical dose of 400 mg. Pralsetinib induced hyperphosphatemia (rats) and multi-organ mineralization (rats and monkeys) in 13-week toxicology studies at exposures approximately 2.8 times and ≥ 0.13 times, respectively, the human exposure based on AUC at the clinical dose of 400 mg.

14 CLINICAL STUDIES

14.1 Metastatic *RET* Fusion-Positive Non-Small Cell Lung Cancer

The efficacy of GAVRETO was evaluated in patients with *RET* fusion-positive metastatic NSCLC in a multicenter, non-randomized, open-label, multi-cohort clinical trial (ARROW, NCT03037385). 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. Identification of a *RET* gene fusion was determined by local laboratories using next generation sequencing (NGS), fluorescence in situ hybridization (FISH), and other tests. Among the 237 patients in the efficacy population(s) described in this section, samples from 40% of patients were retrospectively tested with the Life Technologies Corporation Oncomine Dx Target Test (ODxTT). Patients with asymptomatic central nervous system (CNS) metastases, including patients with stable or decreasing steroid use within 2 weeks prior to study entry, were enrolled. Patients received GAVRETO 400 mg orally once 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) according to RECIST v1.1.

Metastatic *RET* Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy

Efficacy was evaluated in 130 patients with *RET* fusion-positive NSCLC with measurable disease who were previously treated with platinum chemotherapy enrolled into a cohort of ARROW.

The median age was 59 years (range: 26 to 85); 51% were female, 40% were White, 50% were Asian, 4.6% were Hispanic/Latino. ECOG performance status was 0-1 (95%) or 2 (3.8%), 99% of patients had metastatic disease, and 41% had either a history of or current CNS metastasis. Patients received a median of 2 prior systemic therapies (range 1-6); 42% had prior anti-PD-1/PD-L1 therapy and 27% had prior kinase inhibitors. A total of 48% of the patients received prior radiation therapy. *RET* fusions were detected in 80% of patients using NGS (37% tumor samples; 15% blood or plasma samples, 28% unknown), 13% using FISH, and 2% using other methods. The most common *RET* fusion partners were KIF5B (70%) and CCDC6 (19%).

Efficacy results for *RET* fusion-positive NSCLC patients who received prior platinum-based chemotherapy are summarized in Table 10.

Table 10: Efficacy Results in ARROW (Metastatic *RET* Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy)

Efficacy Parameter	GAVRETO N=130
Overall Response Rate (ORR)* (95% CI)	63 (54, 71)
Complete Response, %	6
Partial Response, %	57
Duration of Response (DOR)	N=82
Median, months (95%CI)	38.8 (14.8, NE)
Patients with DOR \geq 12-months [†] , %	66

NE = not estimable

* Confirmed overall response rate assessed by BICR

† Based on observed duration of response

For the 54 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% (95% CI: 45, 72) and the median DOR was 22.3 months (95% CI: 8.0, NE).

Among the 130 patients with *RET*-fusion positive NSCLC, 10 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 7 of these 10 patients including 2 patients with a CNS complete response; 71% of responders had a DOR of \geq 6 months.

Treatment-naïve *RET* Fusion-Positive NSCLC

Efficacy was evaluated in 107 patients with treatment-naïve *RET* fusion-positive NSCLC with measurable disease enrolled into ARROW.

The median age was 62 years (range 30 to 87); 53% were female, 49% were White, 45% were Asian, and 2.8% were Hispanic or Latino. ECOG performance status was 0-1 for 99% of the patients and 98% of patients had metastatic disease; 28% had either history of or current CNS metastasis. *RET* fusions were detected in 68% of patients using NGS (30% tumor samples; 17% blood or plasma; 22% unknown) and 19% using FISH. The most common *RET* fusion partners were *KIF5B* (71%) and *CCDC6* (18%).

Efficacy results for treatment-naïve *RET* fusion-positive NSCLC are summarized in Table 11.

Table 11: Efficacy Results for ARROW (Treatment-Naïve Metastatic *RET* Fusion-Positive NSCLC)

Efficacy Parameter	GAVRETO N=107
---------------------------	--------------------------

Overall Response Rate (ORR)* (95% CI)	78 (68, 85)
Complete Response, %	7
Partial Response, %	71
Duration of Response (DOR)	N=83
Median, months (95% CI)	13.4 (9.4, 23.1)
Patients with DOR \geq 12-months [†] , %	45

* Confirmed overall response rate assessed by BICR

† Based on observed duration of response

14.2 RET Fusion-Positive Thyroid Cancer

The efficacy of GAVRETO was evaluated in *RET* fusion-positive metastatic thyroid cancer patients in a multicenter, open-label, multi-cohort clinical trial (ARROW, NCT03037385). 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 (89% NGS tumor samples and 11% using FISH).

The median age was 61 years (range: 46 to 74); 67% were male, 78% were White, 22% were Asian, 11% were Hispanic/Latino. All patients (100%) had papillary thyroid cancer. ECOG performance status was 0-1 (100%), all patients (100%) had metastatic disease, and 56% had a history of CNS metastases. Patients had received a median of 2 prior therapies (range 1-8). Prior systemic treatments included prior radioactive iodine (100%) and prior sorafenib and/or lenvatinib (56%).

Efficacy results are summarized in Table 12.

Table 12: Efficacy Results for RET Fusion-Positive Thyroid Cancer (ARROW)

Efficacy Parameters	GAVRETO N=9
Overall Response Rate (ORR)* (95% CI)	89 (52, 100)
Complete Response, %	0
Partial Response, %	89
Duration of Response (DOR)	N=8
Median in months (95% CI)	NR (NE, NE)
Patients with DOR \geq 6 months [†] , %	100

NR = Not Reached; NE = Not Estimable

* Confirmed overall response rate assessed by BICR

† Based on observed duration of response

16 HOW SUPPLIED/STORAGE AND HANDLING

GAVRETO (pralsetinib) 100 mg, light blue, opaque, immediate release, hydroxypropyl methylcellulose (HPMC) hard capsule printed with "BLU-667" on the capsule shell body and "100 mg" on the capsule shell cap are supplied as follows:

- Bottles of 60 capsules (NDC 50242-210-60).
- Bottles of 90 capsules (NDC 50242-210-90).

- Bottles of 120 capsules (NDC 50242-210-12).

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [see *USP Controlled Room Temperature*]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

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

ILD/Pneumonitis

Advise patients to contact their healthcare provider if they experience new or worsening respiratory symptoms [see *Warnings and Precautions (5.1)*].

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 [see *Warnings and Precautions (5.2)*].

Hepatotoxicity

Advise patients that hepatotoxicity can occur and to immediately contact their healthcare provider for signs or symptoms of hepatotoxicity [see *Warnings and Precautions (5.3)*].

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 [see *Warnings and Precautions (5.4)*].

Tumor Lysis Syndrome

Advise patients to contact their healthcare provider promptly to report any signs and symptoms of TLS [see *Warnings and Precautions (5.5)*].

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 [see *Warnings and Precautions (5.6)*].

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.7)*, *Use in Specific Populations (8.1)*].

Advise females of reproductive potential to use effective non-hormonal contraception during the treatment with GAVRETO and for 2 weeks after the last dose [see *Use in Specific Populations (8.3)*].

Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the last dose [see *Use in Specific Populations (8.3)*].

Lactation

Advise women not to breastfeed during treatment with GAVRETO and for 1 week after the last dose [see *Use in Specific Populations (8.2)*].

Infertility

Advise males and females of reproductive potential that GAVRETO may impair fertility [See *Use in Specific Populations (8.3)*].

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 [see *Drug Interactions (7.1)*].

Administration

Advise patients to take GAVRETO on an empty stomach (no food intake for at least 2 hours before and at least 1 hour after taking GAVRETO) [see *Dosage and Administration (2.2)*].

GAVRETO[®] [pralsetinib]

Manufactured for:

Genentech, Inc.

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-4990

Jointly marketed by: Genentech USA, Inc. and Blueprint Medicines Corporation

GAVRETO[®] is a registered trademark of Blueprint Medicines Corporation.

© 2023 Genentech, Inc.

© 2023 Blueprint Medicines Corporation

PATIENT INFORMATION

GAVRETO[®] (gav-REH-toh)
(pralsetinib)
capsules

What is GAVRETO?

GAVRETO is a prescription medicine used to treat certain cancers caused by abnormal rearranged during transfection (RET) genes in:

- adults with non-small cell lung cancer (NSCLC) that has spread.
- adults and children 12 years of age and older with advanced thyroid cancer or thyroid cancer that has spread who require a medicine by mouth or injection (systemic therapy) and who have received radioactive iodine and it did not work or is no longer working.

Your healthcare provider will perform a test to make sure that GAVRETO is right for you. It is not known if GAVRETO is safe and effective when used to treat cancers caused by abnormal RET genes:

- in children for the treatment of NSCLC **or**
- in children younger than 12 years of age for the treatment of thyroid cancer.

Before taking GAVRETO, tell your healthcare provider about all of your medical conditions, including if you:

- have lung or breathing problems other than lung cancer
- have high blood pressure
- have bleeding problems
- have liver problems
- plan to have surgery. You should stop taking GAVRETO at least 5 days before your planned surgery. See "**What are the possible side effects of GAVRETO?**"
- are pregnant or plan to become pregnant. GAVRETO can harm your unborn baby.

Females who are able to become pregnant:

- Your healthcare provider will do a pregnancy test before you start treatment with GAVRETO.
- You should use an effective form of non-hormonal birth control (contraception) during treatment and for **2 weeks** after your last dose of GAVRETO.
- Birth control methods that contain hormones (such as birth control pills, injections or transdermal system patches) may not work as well during treatment with GAVRETO.
- Talk to your healthcare provider about birth control methods that may be right for you during this time.
- Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with GAVRETO.

Males with female partners who are able to become pregnant:

- You should use effective birth control (contraception) during treatment and for **1 week** after your last dose of GAVRETO.
- are breastfeeding or plan to breastfeed. It is not known if GAVRETO passes into your breast milk. Do not breastfeed during treatment and for **1 week** after your last dose of GAVRETO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking GAVRETO with other medicines may affect how GAVRETO works.

How should I take GAVRETO?

- Take GAVRETO exactly as your healthcare provider tells you to take it.
- Take your prescribed dose of GAVRETO 1 time each day.
- Take GAVRETO on an empty stomach. **Do not** eat for at least 2 hours before and at least 1 hour after taking GAVRETO.
- **Do not** change your dose or stop taking GAVRETO unless your healthcare provider tells you to.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with GAVRETO if you develop side effects.
- If you miss a dose of GAVRETO, take it as soon as possible on the same day. Then take your next dose of GAVRETO at your regular time the next day.
- If you vomit after taking a dose of GAVRETO, do not take an extra dose. Take your next dose of GAVRETO at your regular time the next day.

What are the possible side effects of GAVRETO?

GAVRETO may cause serious side effects, including:

- **Lung problems.** GAVRETO may cause severe or life-threatening inflammation of the lungs during treatment, that can lead to death. Tell your healthcare provider right away if you have any new or worsening symptoms, including:
 - shortness of breath
 - cough
 - fever
- **High blood pressure (hypertension).** High blood pressure is common with GAVRETO and may sometimes be severe. You should check your blood pressure regularly during treatment with GAVRETO. Tell your healthcare provider if you have increased blood pressure readings or get any symptoms of high blood pressure, including:
 - confusion
 - headaches
 - shortness of breath
 - dizziness
 - chest pain
- **Liver problems.** Liver problems (increased liver function blood test results) can happen during treatment with GAVRETO and may sometimes be serious. Your healthcare provider will do blood tests before and during treatment with GAVRETO to check you for liver problems. Tell your healthcare provider right away if you get any signs or symptoms of liver problem during treatment, including:
 - yellowing of your skin or the white part of your eyes (jaundice)
 - dark "tea-colored" urine
 - sleepiness
 - bleeding or bruising
 - loss of appetite
 - nausea or vomiting
 - pain on the upper right side of your stomach area
- **Bleeding problems.** GAVRETO can cause bleeding which can be serious and cause death. Tell your healthcare provider if you have any signs or symptoms of bleeding during treatment, including:
 - vomiting blood or if your vomit looks like coffee grounds
 - pink or brown urine
 - red or black (looks like tar) stools
 - coughing up blood or blood clots
 - unusual bleeding or bruising of your skin
 - menstrual bleeding that is heavier than normal
 - unusual vaginal bleeding
 - nose bleeds that happen often
 - drowsiness or difficulty being awakened
 - confusion
 - headache
 - change in speech
- **Tumor lysis syndrome (TLS).** TLS is caused by a fast breakdown of cancer cells. TLS can cause you to have kidney failure and the need for dialysis treatment, an abnormal heartbeat, and may sometimes lead to hospitalization. Your healthcare provider may do blood tests to check you for TLS. You should stay well hydrated during treatment with GAVRETO. Call your healthcare provider or get emergency medical help right away if you develop any of these symptoms during treatment with GAVRETO:

- nausea
 - vomiting
 - weakness
 - swelling
 - shortness of breath
 - muscle cramps
 - seizures
- **Risk of wound healing problems.** Wounds may not heal properly during treatment with GAVRETO. Tell your healthcare provider if you plan to have any surgery before or during treatment with GAVRETO.
 - You should not take GAVRETO for at least 5 days before surgery.
 - Your healthcare provider should tell you when you may start taking GAVRETO again after surgery.

The most common side effects of GAVRETO include:

- muscle and joint pain
- constipation
- diarrhea
- tiredness
- swelling of your face, arms, legs, hands, and feet (edema)
- fever
- cough

The most common severe abnormal blood test results with GAVRETO include:

- decreased white blood cell, red blood cell, and platelet counts
- decreased levels of phosphate, body salt (sodium), calcium and potassium in the blood
- abnormal liver function blood tests
- increased levels of enzyme called alkaline phosphatase in the blood (test for liver or bone problems)
- increased levels of potassium in the blood

GAVRETO may affect fertility in males and females, which may affect your ability to have children. Talk to your healthcare provider if this is a concern for you.

These are not all the possible side effects of GAVRETO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store GAVRETO?

- Store GAVRETO at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect GAVRETO from moisture.

Keep GAVRETO and all medicines out of the reach of children.

General information about the safe and effective use of GAVRETO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use GAVRETO for a condition for which it was not prescribed. Do not give GAVRETO to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about GAVRETO that is written for health professionals.

What are the ingredients in GAVRETO?

Active ingredient: pralsetinib

Inactive ingredients: citric acid, hydroxypropyl methylcellulose (HPMC), magnesium stearate, microcrystalline cellulose (MCC), pregelatinized starch and sodium bicarbonate.

Capsule shell: FD&C Blue #1 (Brilliant Blue FCF), hypromellose and titanium dioxide.
White printing ink: butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution and titanium dioxide.

Manufactured for: **Genentech, Inc.**, A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990

Jointly marketed by: Genentech USA, Inc. and Blueprint Medicines Corporation

GAVRETO[®] is a registered trademark of Blueprint Medicines Corporation.

© 2023 Genentech, Inc.

© 2023 Blueprint Medicines Corporation.

For more information, go to www.GAVRETO.com or call 1-888-835-2555.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: 08/2023

Representative sample of labeling (see the HOW SUPPLIED section for complete listing):

PRINCIPAL DISPLAY PANEL - 100 mg Capsule Bottle Label

NDC 50242-210-60

Gavreto[®]
(pralsetinib)
capsules

100 mg

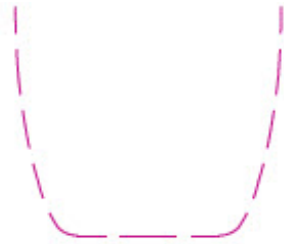
For Oral Use

Rx only

60 Capsules

Genentech
blueprint[™]
MEDICINES

10242131



NDC 50242-210-60

Gavreto[®]
(pralsetinib)
capsules

100 mg

For Oral Use

R_x only

60 Capsules

Genentech

 **blueprint**[™]
MEDICINES

10242131

GAVRETO

pralsetinib capsule

Product Information

Product Type

HUMAN PRESCRIPTION DRUG

Item Code (Source)

NDC:50242-210

Route of Administration	ORAL
--------------------------------	------

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
PRALSETINIB (UNII: 1WPE73O1W) (PRALSETINIB - UNII:1WPE73O1W)	PRALSETINIB	100 mg

Inactive Ingredients

Ingredient Name	Strength
HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 9XZ8H6N6OH)	
SODIUM BICARBONATE (UNII: 8MDF5V39QO)	
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics

Color	BLUE (light blue)	Score	no score
Shape	CAPSULE	Size	11mm
Flavor		Imprint Code	BLU667
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50242-210-90	1 in 1 CARTON	07/01/2021	
1		90 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:50242-210-60	1 in 1 CARTON	07/01/2021	
2		60 in 1 BOTTLE; Type 0: Not a Combination Product		
3	NDC:50242-210-83	1 in 1 CARTON	07/01/2021	
3		60 in 1 BOTTLE; Type 0: Not a Combination Product		
4	NDC:50242-210-12	1 in 1 CARTON	09/28/2022	
4		120 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA213721	07/01/2021	

Labeler - Genentech, Inc. (080129000)

Registrant - Genentech, Inc. (080129000)

Revised: 8/2023

Genentech, Inc.