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

INDICATIONS AND USAGE

GAVRETO is a kinase inhibitor 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. (1)

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)

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 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)
- 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. (5.5)
- 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. (5.6, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (≥25%) were fatigue, constipation, musculoskeletal pain, and hypertension. The most common Grade 3-4 laboratory abnormalities (≥2 %) were decreased lymphocytes, decreased neutrophils, decreased phosphate, decreased hemoglobin, decreased sodium, decreased calcium (corrected), and increased alanine aminotransferase (ALT). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Blueprint Medicines Corporation at 1-888-258-7768 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Strong CYP3A inhibitors: Avoid coadministration. (7.1)
- Combined P-gp and Strong CYP3A inhibitors: Avoid coadministration. If coadministration cannot be avoided, reduce the dose of GAVRETO. (2.4, 7.1, 12.3)
- Strong 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)

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

Revised: 9/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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.

This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14)]*. 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 *[see Clinical Studies (14)]*. Information on FDA-approved tests is available at http://www.fda.gov/CompanionDiagnostics.

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
ILD/Pneumonitis *[see Warnings and Precautions (5.1)]*	Grade 1 or 2	Withhold GAVRETO until resolution. Resume by reducing the dose as shown in Table 1. Permanently discontinue GAVRETO for recurrent ILD/pneumonitis.
	Grade 3 or 4	Permanently discontinue for confirmed ILD/pneumonitis.
Hypertension *[see Warnings and Precautions (5.2)]*	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 *[see Warnings and Precautions (5.3)]*	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 *[see Warnings and Precautions (5.4)]*	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 *[see Adverse Reactions 6.1]*	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

2.4 Dose Modification for Use with Combined P-glycoprotein (P-gp) and Strong CYP3A Inhibitors

Avoid coadministration of GAVRETO with known combined P-gp and strong CYP3A inhibitors. If coadministration with a combined P-gp and strong CYP3A inhibitor 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 combined P-gp and strong CYP3A inhibitor *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

Table 3: 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

2.5 Dose Modification for Use with Strong CYP3A Inducers

Avoid coadministration of GAVRETO with strong CYP3A inducers. If coadministration with a strong CYP3A inducer 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 *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

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 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 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 29% of patients, including Grade 3 hypertension in 14% of patients *[see Adverse Reactions (6.1)]*. 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 *[see Dosage and Administration (2.3)]*.

5.3 Hepatotoxicity

Serious hepatic adverse reactions occurred in 2.1% of patients treated for GAVRETO. Increased AST occurred in 69% of patients, including Grade 3 or 4 in 5.4% and increased ALT occurred in 46% of patients, including Grade 3 or 4 in 6% *[see Adverse Reactions (6.1)]*. 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 *[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 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 *[see Dosage and Administration (2.3)]*.

5.5 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.

5.6 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 embryolethality 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 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 *[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)]*
- Risk of Impaired Wound Healing *[see Warnings and Precautions (5.5)]*

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 438 patients with *RET* altered solid tumors in ARROW *[see Clinical Studies (14)]*. Among 438 patients who received GAVRETO, 47% were exposed for 6 months or longer and 23% were exposed for greater than one year.

<u>*RET* Fusion-Positive Non-Small Cell Lung Cancer</u>

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 220 patients with metastatic rearranged during transfection (*RET* fusion-positive) non-small cell lung cancer (NSCLC) in ARROW *[see Clinical Studies (14)]*.

The median age was 60 years (range: 26 to 87 years); 52% were female, 50% were White, 41% were Asian, and 4% were Hispanic/Latino.

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).

Permanent discontinuation due to an adverse reaction occurred in 15% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation included pneumonitis (1.8%), pneumonia (1.8%), and sepsis (1%).

Dosage interruptions due to an adverse reaction occurred in 60% of patients who received GAVRETO. 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.

Dose reductions due to adverse reactions occurred in 36% of patients who received GAVRETO. Adverse reactions requiring dosage reductions in ≥ 2% of patients included neutropenia, anemia, pneumonitis, neutrophil count decreased, fatigue, hypertension, pneumonia, and leukopenia.

The most common adverse reactions (≥25%) were fatigue, constipation, musculoskeletal pain, and hypertension. The most common Grade 3-4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased neutrophils, decreased phosphate, decreased hemoglobin, decreased sodium, decreased calcium (corrected), and increased alanine aminotransferase (ALT).

Table 4 summarizes the adverse reactions in ARROW.

Table 4: Adverse Reactions (≥ 15%) in Patients Who Received GAVRETO in ARROW

Adverse Reactions	GAVRETO N=220	
	Grades 1-4 (%)	Grades 3-4 (%)
General		
Fatigue[1]	35	2.3*
Pyrexia	20	0
Edema[2]	20	0
Gastrointestinal		
Constipation	35	1*
Diarrhea[3]	24	3.2*
Dry Mouth	16	0
Musculoskeletal Disorders		
Musculoskeletal Pain[4]	32	0
Vascular		
Hypertension[5]	28	14*
Respiratory, thoracic and mediastinal		
Cough[6]	23	0.5*
Infections		
Pneumonia[7]	17	8

1 Fatigue includes fatigue, asthenia
2 Edema includes edema peripheral, face edema, periorbital edema, eyelid edema, edema generalized, swelling
3 Diarrhea includes diarrhea, colitis, enteritis
4 Musculoskeletal pain includes back pain, myalgia, arthralgia, pain in extremity, musculoskeletal pain, neck pain, musculoskeletal chest pain, bone pain, musculoskeletal stiffness, arthritis, spinal pain
5 Hypertension includes hypertension, blood pressure increased
6 Cough includes cough, productive cough, upper-airway cough syndrome
7 Pneumonia includes pneumonia, atypical pneumonia, lung infection, pneumocystis jirovecii pneumonia, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia influenza, pneumonia streptococcal
*Only includes a Grade 3 adverse reaction

Table 5 summarizes the laboratory abnormalities in ARROW.

Table 5: Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in Patients Who Received GAVRETO in ARROW

Laboratory Abnormality	GAVRETO N=220	
	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry		
Increased AST	69	1.1
Increased ALT	46	2.1
Increased creatinine	42	1.1
Increased alkaline phosphatase	40	1.1
Decreased calcium (corrected)	29	2.2
Decreased sodium	27	3.2
Decreased phosphate	27	9
Hematology		
Decreased hemoglobin	54	5
Decreased lymphocytes	52	20
Decreased neutrophils	52	10
Decreased platelets	26	0

Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 83 to 94 patients.

Clinically relevant laboratory abnormalities < 20% of patients who received GAVRETO included hyperphosphatemia (10%).

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on GAVRETO

Strong CYP3A Inhibitors

Avoid coadministration with strong CYP3A inhibitors. Coadministration of GAVRETO with a strong CYP3A inhibitor increases pralsetinib exposure, which may increase the incidence and severity of adverse reactions of GAVRETO.

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 *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

Strong CYP3A Inducers

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

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 embryolethality 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 1.5-2.2 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 0.5 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 final dose.

8.3 Females and Males of Reproductive Potential

Based on animal data, GAVRETO can cause embryolethality 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 final 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 final 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 not been established in pediatric patients.

Animal Toxicity Data

In a 4-week repeat-dose toxicology study in non-human primates, physeal 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 physeal 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 physeal thickness in the femur and incisor degeneration did not show evidence of complete recovery in the 28-day rat study

8.5 Geriatric Use

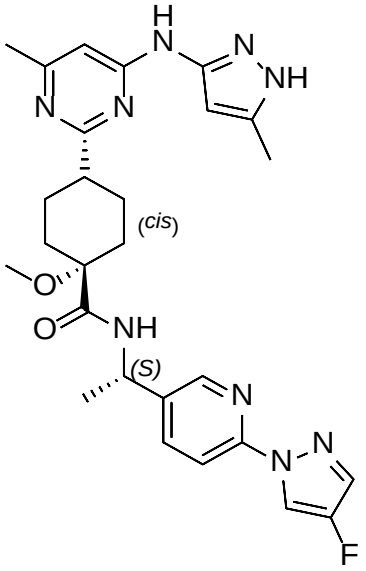
Of the 438 patients in ARROW who received the recommended dose of GAVRETO at 400 mg once daily, 30% were 65 years or older. No overall differences in pharmacokinetics (PK), safety or efficacy were observed in comparison with younger patients.

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 $C_{27}H_{32}FN_9O_2$, 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 Cmax. 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 GAVRETO was assessed in 34 patients with *RET* fusion-positive solid tumors administered at the recommended dosage. No large mean increase in QTc (> 20 ms) was detected in the study.

12.3 Pharmacokinetics

At 400 mg 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 ($AUC_{0\text{-}24h}$) of pralsetinib was 2830 (52.5%) ng/mL and 43900 (60.2%) 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 < 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 400 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) $AUC_{0\text{-}INF}$ 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 (Vd/F) of pralsetinib is 228 L (75%). 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 (±standard deviation) plasma elimination half-life ($T_{½}$) of pralsetinib 14.7 hours (6.5) following single doses and 22.2 hours (13.5) following multiple doses of pralsetinib. The mean (CV%) apparent oral clearance (CL/F) of pralsetinib is 9.1 L/h (60%) 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 approximately 310 mg of radiolabeled pralsetinib to healthy subjects, pralsetinib metabolites from oxidation (M531, M453, M549b) and glucuronidation (M709) were detected as 5% or less.

Excretion

Approximately 73% (66% as unchanged) of the total administered radioactive dose [^{14}C] 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 (18 to 87 years), sex, race (256 White, 2 Black, or 147 Asian), and body weight (29.5 to 149 kg). Mild and moderate renal impairment (CLcr 30 - 89 mL/min) had no effect on the exposure of pralsetinib. Pralsetinib has not been studied in patients with severe renal impairment (CLcr < 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 Approaches

Combined P-gp and Strong CYP3A Inhibitors: Coadministration of itraconazole 200 mg once daily with a single GAVRETO 200 mg dose increased pralsetinib C_{max} by 84% and $AUC_{0\text{-}INF}$ by 251%.

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

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 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 2.5-3.6 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 at 5 mg/kg (approximately 0.3 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 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 0.9 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 ≥1.1 times and ≥2.6 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 2.4-3.5 times and ≥0.11 times, respectively, the human exposure based on AUC at the clinical dose of 400 mg.

14 CLINICAL STUDIES

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 114 patients in the efficacy population(s) described in this section, samples from 59% 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 400mg 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.

<u>Metastatic *RET* Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy</u>

Efficacy was evaluated in 87 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 60 years (range: 28 to 85); 49% were female, 53% were White, 35% were Asian, 6% were Hispanic/Latino. ECOG performance status was 0-1 (94%) or 2 (6%), 99% of patients had metastatic disease, and 43% had either a history of or current CNS metastasis. Patients received a median of 2 prior systemic therapies (range 1–6); 45% had prior anti-PD-1/PD-L1 therapy and 25% had prior kinase inhibitors. A total of 52% of the patients received prior radiation therapy. *RET* fusions were detected in 77% of patients using NGS (45% tumor samples; 26% blood or plasma samples, 6% unknown), 21% using FISH, and 2% using other methods. The most common *RET* fusion partners were KIF5B (75%) and CCDC6 (17%).

Efficacy results for *RET* fusion-positive NSCLC patients who received prior platinum-based chemotherapy are summarized in Table 6

Table 6: Efficacy Results in ARROW (Metastatic *RET* Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy)

Efficacy Parameter	**GAVRETO (N=87)**
Overall Response Rate (ORR)[a] (95% CI)	57 (46, 68)
Complete Response, %	5.7
Partial Response, %	52
Duration of Response (DOR)	(N=50)
Median, months(95%CI)	NE (15.2-NE)
Patients with DOR ≥ 6-months[b], %	80

NE = not estimable
a Confirmed overall response rate assessed by BICR
b Calculated using the proportion of responders with an observed duration of response at least 6 months or greater

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% (95% CI: 42, 74) and the median DOR was not reached (95% CI: 11.3, NE).

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.

Treatment-naïve *RET* Fusion-Positive NSCLC

Efficacy was evaluated in 27 patients with treatment-naïve *RET* fusion-positive NSCLC with measurable disease enrolled into ARROW.

The median age was 65 years (range 30 to 87); 52% were female, 59% were White, 33% were Asian, and 4% were Hispanic or Latino. ECOG performance status was 0-1 for 96% of the patients and all patients (100%) had metastatic disease 37% had either history of or current CNS metastasis. *RET*-fusions were detected in 67% of patients using NGS (41% tumor samples; 22% blood or plasma; 4% unknown) and 33% using FISH. The most common *RET* fusion partners were *KIF5B* (70%) and *CCD6* (11%).

Efficacy results for treatment-naïve *RET* fusion-positive NSCLC are summarized in Table 7.

Table 7: Efficacy Results for ARROW (Treatment-Naïve Metastatic *RET* Fusion-Positive NSCLC

Efficacy Parameter	**GAVRETO (N=27)**
Overall Response Rate (ORR)[a] (95% CI)	70 (50, 86)
Complete Response, %	11
Partial Response, %	59
Duration of Response (DOR)	**(N=19)**
Median, months (95% CI)	9.0 (6.3, NE)
Patients with DOR ≥ 6-months[b], %	58

NE = not estimable
a Confirmed overall response rate assessed by BICR
b Calculated using the proportion of responders with an observed duration of response at least 6 months or greater

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 72064-210-60).
- Bottles of 90 capsules (NDC 72064-210-90).
- Bottles of 120 capsules (NDC 72064-210-12).

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)*.

<u>ILD/Pneumonitis</u>

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

<u>Hypertension</u>

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)]*.

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 (5.5)]*.

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 (5.6), 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 final *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 final dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with GAVRETO and for 1 week after the final 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, at least 1 hour before and at least 2 hours after a meal *[see Dosage and Administration (2.2)]*.

Manufactured for:

Blueprint Medicines Corporation, 45 Sidney Street, Cambridge, MA 02139, USA

PATIENT INFORMATION
GAVRETO™ (gav-REH-toh)
(pralsetinib) capsules

What is GAVRETO?

GAVRETO is a prescription medicine used to treat adults with non-small cell lung cancer (NSCLC) that:

- has spread to other parts of the body (metastatic), **and**
- is caused by abnormal rearranged during transfection (RET) genes. 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 in children.

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
- plan to have 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 final 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 final 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 final dose of GAVRETO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. GAVRETO may affect the way other medicines work, and 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
- **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:

- tiredness
- constipation
- muscle and joint painhigh blood pressure
- decreased white blood cell and red blood cell counts
- decreased levels of phosphate in the blood
- decreased levels of body salt (sodium) in the blood
- decreased levels of calcium in the blood
- abnormal liver function blood tests

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 of 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: Blueprint Medicines Corporation, Cambridge, MA 02139, USA

For more information, go to www.GAVRETO.com or call 1-888-258-7768.

This Patient Information has been approved by the U.S. Food and Drug Administration Issued September 2020