PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrGAVRETO®

pralsetinib capsules

Capsules, 100 mg pralsetinib, Oral

Protein Kinase Inhibitor (L01EX)

GAVRETO, indicated for:

- the treatment of adult patients with rearranged during transfection (*RET*) fusion-positive locally advanced unresectable or metastatic non-small cell lung cancer (NSCLC).

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for GAVRETO please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

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What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

1 Indications, 1.2 Geriatrics	05/2024
4 Dosage and Administration, 4.1 Dosing Considerations	05/2024
4 Dosage and Administration , 4.2 Recommended Dose and Dosage Adjustment	11/2024
7 Warnings and Precautions, Cardiovascular	05/2024
7 Warnings and Precautions, Hepatic	05/2024
7 Warnings and Precautions, Reproductive Health: Female and Male Potential	05/2024
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7 Warnings and Precautions, 7.1.4 Geriatrics	05/2024

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NOC/c GAVRETO® (pralsetinib) is indicated for the treatment of adult patients with rearranged during transfection (*RET*) fusion-positive locally advanced unresectable or metastatic non-small cell lung cancer (NSCLC).

A validated test is required prior to treatment to identify *RET* fusion-positive status (see 7 WARNINGS AND PRECAUTIONS: *RET* testing).

Efficacy in patients with *RET* fusion-positive NSCLC was based on objective response rate and duration of response in a single-arm study (see 14 CLINICAL TRIALS).

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age): Of the 540 patients in ARROW who received the recommended dose of GAVRETO at 400 mg once daily, 30.9% were 65 years or older. No overall differences in pharmacokinetics (PK) or efficacy were observed in comparison with younger patients. Patients ≥65 years of age were more likely to experience adverse events, serious adverse events, grade 3/4/5 adverse events, grade 3/4/5 serious adverse events, treatment interruptions, or treatment discontinuations.

2 CONTRAINDICATIONS

NOC/c GAVRETO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- GAVRETO may cause fetal harm when administered to a pregnant woman (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women)
- GAVRETO may cause pneumonitis/interstitial lung disease (ILD) (see 7 WARNINGS AND PRECAUTIONS)
- GAVRETO may cause serious hypertension (see 7 WARNINGS AND PRECAUTIONS)
- GAVRETO may cause serious hepatotoxicity (see 7 WARNINGS AND PRECAUTIONS)
- GAVRETO may cause serious hemorrhagic events (see 7 WARNINGS AND PRECAUTIONS)
- GAVRETO may impair wound healing (see 7 WARNINGS AND PRECAUTIONS)

Treatment with GAVRETO (pralsetinib) should be initiated and supervised by a qualified physician experienced in the use of anticancer therapies (see 1 INDICATIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Coadministration of pralsetinib with moderate – strong CYP3A4 and/or P-gp inhibitors may increase pralsetinib plasma concentrations, which may increase the risk of adverse reactions. Avoid coadministration of GAVRETO with moderate – strong CYP3A4 and/or P-gp inhibitors. If coadministration cannot be avoided, reduce the GAVRETO dose (see 4.2 Recommended Dose and Dosage Adjustment and 9 DRUG INTERACTIONS).
- Coadministration of pralsetinib with a strong or moderate CYP3A4 inducer may decrease pralsetinib plasma concentrations and may result in decreased efficacy of pralsetinib. Avoid coadministration of GAVRETO with strong or moderate CYP3A4 inducers. If coadministration cannot be avoided, increase the GAVRETO dose (see 4.2 Recommended Dose and Dosage Adjustment and 9 DRUG INTERACTIONS).

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

The recommended dose of GAVRETO is 400 mg (four 100 mg capsules) taken orally once daily on an empty stomach (no food intake for at least 2 hours before and at least 1 hour after taking GAVRETO). Continue treatment as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity.

Dosage Adjustment

If dose modifications are required for adverse reactions, reduce the dose in 100 mg (one capsule) increments; the lowest recommended dose of GAVRETO is 100 mg once daily. GAVRETO dose reductions for adverse reactions are summarized in Table 1.

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

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

Recommended dose modifications of GAVRETO for the management of specific adverse reactions are provided in Table 2.

Table 2: Recommended Dose Modifications for GAVRETO for 8 ADVERSE REACTIONS

Adverse Reaction	Severity[a]	Dosage Modification
ILD/Pneumonitis (see 7 WARNINGS AND PRECAUTIONS)	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 GAVRETO for confirmed ILD/pneumonitis.[b]
Hypertension (see 7 WARNINGS AND PRECAUTIONS)	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	Permanently discontinue GAVRETO.
Hepatotoxicity (see 7 WARNINGS AND PRECAUTIONS)	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, permanently discontinue GAVRETO.
Hemorrhagic Events (see 7 WARNINGS AND PRECAUTIONS)	Grade 3	Withhold GAVRETO until recovery to ≤ Grade 1. Resume by reducing the dose as shown in Table 1. If hemorrhagic events recur at Grade 3 or higher, permanently discontinue GAVRETO.
	Grade 4	Permanently discontinue GAVRETO.
QT Interval Prolongation (see 7 WARNINGS AND PRECAUTIONS)	Grade 3	Interrupt treatment with GAVRETO for QTc intervals >500ms until QTc interval returns to <470ms. Resume at the same dose if risk factors that cause QT prolongation are identified and corrected. Resume treatment at a reduced dose if other risk factors that cause QT prolongation are not identified.
	Grade 4	Permanently discontinue GAVRETO if the patient has life-threatening arrhythmia.
Other Clinically Relevant Adverse Reactions (see 8 ADVERSE REACTIONS)	Grade 3 or 4	Withhold GAVRETO until improvement to ≤ Grade 2. Resume at reduced dose (Table 1). Withhold GAVRETO until improvement to ≤ Grade 2 for recurrent Grade 3 events. Resume at reduced dose (Table 1). Permanently discontinue GAVRETO for recurrent Grade 4 events.

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

[b] *Not attributable to non-small cell lung cancer (NSCLC) progression, other pulmonary disease, infection, or radiation effect.*

Dose Modification for Use with Cytochrome P450 (CYP) 3A4 and/or P-glycoprotein (P-gp) Inhibitors

Avoid concomitant use of GAVRETO with any of the following:

- Strong CYP3A4 inhibitors
- Moderate CYP3A4 inhibitors
- P-gp inhibitors
- Combined P-gp and strong CYP3A4 inhibitors
- Combined P-gp and moderate CYP3A4 inhibitors

If concomitant use with any of the above inhibitors cannot be avoided, reduce the current dose of GAVRETO as recommended in Table 3 below. After the coadministered inhibitor has been discontinued for 3-5 elimination half-lives, resume GAVRETO at the dose taken prior to initiating the inhibitor [see 9 DRUG INTERACTIONS].

Table 3: Recommended Dose Modifications for GAVRETO for Coadministration with CYP3A4 and/or P-gp Inhibitors

Current GAVRETO Dosage	Recommended GAVRETO Dosage when coadministered with:	
	• Combined P-gp and Strong CYP3A4 Inhibitors	• Strong CYP3A4 Inhibitors • Moderate CYP3A4 Inhibitors • P-gp Inhibitors • Combined P-gp and Moderate CYP3A4 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

Dose Modification for Use with CYP3A4 Inducers

Avoid concomitant use of GAVRETO with any of the following:

- Strong CYP3A4 inducers
- Moderate CYP3A4 inducers

If concomitant use with any of the above inducers cannot be avoided, increase the 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 9 DRUG INTERACTIONS].

Table 4: Recommended Dosage Modifications for GAVRETO for Coadministration with CYP3A4 Inducers

Current GAVRETO Dosage	Recommended GAVRETO Dosage when Coadministered with:	
	Strong CYP3A4 Inducers	**Moderate CYP3A4 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

Special Populations

- **Pediatrics (<18 years old):** Health Canada has not authorized an indication for pediatric use.
- **Geriatrics (≥65 years old):** No dose adjustment is required in patients of ≥65 years of age [see 10 CLINICAL PHARMACOLOGY].
- **Renal Impairment:** No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance [CL_{CR}] 30 to 89 mL/min estimated by Cockcroft-Gault).

The recommended dose of GAVRETO has not been established for patients with severe renal impairment (CL_{CR} 15 to 29 mL/min) or end-stage renal disease (CL_{CR} <15 mL/min) [see 10 CLINICAL PHARMACOLOGY].

- **Hepatic Impairment:** No dose adjustment is recommended for patients with mild (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or total bilirubin >1 to 1.5 times ULN and any AST), moderate (total bilirubin > 1.5 to 3.0 times ULN and any AST), or severe (total bilirubin > 3.0 times ULN and any AST) hepatic impairment [see 10 CLINICAL PHARMACOLOGY].

4.3 Reconstitution

Not applicable.

4.4 Administration

GAVRETO is to be taken on an empty stomach (no food intake for at least 2 hours before and at least 1 hour after taking GAVRETO) [see 10 CLINICAL PHARMACOLOGY; 9.5 Drug-Food Interactions]. Continue treatment as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity.

4.5 Missed Dose

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.

GAVRETO is to be taken on an empty stomach (no food intake for at least 2 hours before and at least 1 hour after taking GAVRETO) [see 10 CLINICAL PHARMACOLOGY; 9.5 Drug-Food Interactions].

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

5 OVERDOSAGE

There is limited experience with overdose in clinical trials with GAVRETO. The highest dose of GAVRETO studied in a Phase 1 clinical trial was 600mg QD in 4 patients. No new safety concern was observed. There is no known specific antidote for GAVRETO overdose. In the event of suspected overdose, interrupt GAVRETO, undertake general supportive measures, and observe until clinical stabilization.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 5: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	100 mg pralsetinib capsule	Citric Acid, FD&C Blue #1 (Brilliant Blue FCF), Hydroxypropyl Methylcellulose (HPMC, Hypromellose), Magnesium Stearate, Microcrystalline Cellulose (MCC), Pharmaceutical grade printing ink, Pregelatinized Starch, Sodium Bicarbonate,

		Titanium Dioxide.

Description

GAVRETO (pralsetinib) capsules are supplied as 100 mg, light blue opaque immediate release hydroxypropyl methylcellulose (HPMC) hard capsule, printed with “BLU-667” on the body and “100 mg” on the cap, available in bottles of 60 capsules, 90 capsules, and 120 capsules (not all pack sizes may be marketed).

NOC/c

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

RET Testing

Patients treated with GAVRETO must have a *RET* fusion-positive status based on a validated *RET* assay. Assessment for *RET* fusion-positive locally advanced unresectable or metastatic NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized.

Improper assay performance can lead to unreliable test results.

Carcinogenesis and Mutagenesis

Please see 16 NON-CLINICAL TOXICOLOGY.

Cardiovascular

Hypertension

Of the 540 patients in ARROW who received the recommended dose of GAVRETO at 400 mg once daily, hypertension occurred in 35.0% of patients, including Grade 3-4 hypertension in 17.6% of patients. Overall, 4.8% of patients 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 Table 2, 4 DOSAGE AND ADMINISTRATION].

QT interval prolongation

Prolongation of the QT interval has been observed in patients who received Gavreto in clinical trials. Therefore, before starting Gavreto treatment, patients should have a QTc interval <=470ms and serum electrolytes within normal range. Hypokalaemia, hypomagnesaemia, and hypocalcaemia should be corrected both prior and during Gavreto treatment. Electrocardiograms (ECGs) and serum electrolytes should be monitored before starting and during Gavreto treatment, then periodically, as clinically indicated, depending also on presence of other risk factors (e,g, intercurrent diarrhoea, vomiting, nausea, concomitant medications).

Pralsetinib should be used with caution in patients with medical history of cardiac arrhythmias or QT interval prolongation, as well as in patients on strong CYP 3A4 inhibitors or on medicinal products known to be associated with QT/QTc interval prolongation.

Gavreto may require interruption, dose modification, or discontinuation [see Table 2, 4 DOSAGE AND ADMINISTRATION].

Driving and Operating Machinery

No studies on the effects of GAVRETO on the ability to drive or use machines have been performed. Caution should be exercised when operating a vehicle or potentially dangerous machinery until the patient is reasonably certain that GAVRETO does not affect them adversely.

Hematologic

Hemorrhage

Serious, including fatal, hemorrhagic events can occur with GAVRETO. Of the 540 patients in ARROW who received the recommended dose of GAVRETO at 400 mg once daily, Grade ≥ 3 hemorrhagic events occurred in 4.1% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event.

Withhold, reduce dose or permanently discontinue GAVRETO based on severity [see Table 2, 4 DOSAGE AND ADMINISTRATION].

Hepatic

Of the 540 patients in ARROW who received the recommended dose of GAVRETO at 400 mg once daily, serious hepatic adverse reactions occurred in 1.5% of patients treated for GAVRETO. Increased AST occurred in 49.1% of patients, including Grade 3-4 adverse reactions in 6.9%, and increased ALT occurred in 37.0% of patients, including Grade 3 or 4 adverse reactions in 4.8%.

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 Table 2].

Monitoring and Laboratory Tests

Routine medical follow-up with a certified health care professional, which may include physical exams, laboratory tests, and/or diagnostic imaging, is required while being treated with GAVRETO (see 7 WARNINGS AND PRECAUTIONS: Hepatic; Hypertension, and 8 ADVERSE REACTIONS).

Perform electrocardiograms and measure serum electrolytes before starting and during GAVRETO treatment (see 7 WARNINGS AND PRECAUTIONS, QT interval prolongation)

Reproductive Health: Female and Male Potential

There is no clinical data on the use of GAVRETO during pregnancy. Studies in animals show reproductive toxicity [see 16 NON-CLINICAL TOXICOLOGY and 7.1 Special Populations, 7.1.1 Pregnant Women]

- GAVRETO should not be used during pregnancy, unless clearly necessary and after a careful consideration of the need of the mother and the risk to the fetus.
- Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see 7 WARNINGS AND PRECAUTIONS, Special Populations]
- Pregnancy Testing: Verify pregnancy status of females of reproductive potential prior to initiating GAVRETO.
- Advise females of reproductive potential to use effective non-hormonal contraception during the treatment with GAVRETO and for 2 weeks after the final dose. GAVRETO may render hormonal

contraceptives ineffective.

- Advise male patients with female partners of reproductive potential to use effective contraception, including a barrier method, during treatment with GAVRETO and for at least 1 week after the final dose.

Fertility

There is no clinical data on the effects of pralsetinib on fertility. Based on histopathological findings in the reproductive tissues from male and female rats in a 13-week repeated-dose toxicology study and a dedicated fertility study in which animals of both sexes were treated and mated to each other, GAVRETO may reduce fertility [see 16 NON-CLINICAL TOXICOLOGY].

Teratogenic Risk

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. For specific advice see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential.

Respiratory

Interstitial Lung Disease (ILD)/ Pneumonitis

Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with GAVRETO. Of the 540 patients in ARROW who received the recommended dose of GAVRETO at 400 mg once daily, pneumonitis occurred in 12.2% 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 Table 2, 4 DOSAGE AND ADMINISTRATION].

Risk of Impaired Wound Healing

Impaired wound healing may occur in patients during treatment with drugs that inhibit the vascular endothelial growth factor (VEGF) pathway. GAVRETO has the ability to inhibit the VEGF pathway, and may impair or slow wound healing.

GAVRETO should be discontinued for at least 5 days prior to elective surgery. GAVRETO should not be initiated for at least 14 days following major surgery and until surgical wound is fully healed. The safety of resuming GAVRETO after surgery or after resolution of wound healing complications has not been established.

7.1 Special Populations

7.1.1 Pregnant Women

There is no clinical data on the use of GAVRETO in pregnant women.

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 during the period of organogenesis was teratogenic and embryotoxic in rats at exposures below the human exposures at the 400 mg once daily dose [see 16 NON-CLINICAL TOXICOLOGY].

GAVRETO should not be used during pregnancy, unless clearly necessary and after a careful consideration of the need of the mother and the risk to the fetus.

7.1.2 Breast-feeding

There are no data regarding the presence of pralsetinib or its metabolites in milk, the effects of pralsetinib on the breastfed infant, or its effects on milk production.

It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk precaution should be exercised. Advise lactating women not to breast feed during treatment with GAVRETO and for 1 week following the final dose.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use [see 16 NON-CLINICAL TOXICOLOGY].

7.1.4 Geriatrics

Of the 540 patients in ARROW who received the recommended dose of GAVRETO at 400 mg once daily, 30.9% were 65 years or older. No overall differences in pharmacokinetics (PK), or efficacy were observed in comparison with younger patients.

Safety of GAVRETO was generally consistent between elderly (≥65 years) and younger patients (< 65 years), although a greater percentage of elderly patients compared with younger patients experienced serious adverse events (73.7% for patients ≥65 years vs. 58.4% for patients <65 years of age), Grade ≥3 adverse events (89.8% for patients ≥65 years vs. 78.3% for patients <65 years of age), serious Grade ≥3 adverse events (65.3% for patients ≥65 years vs. 51.7% for patients <65 years of age), adverse events leading to treatment interruption (77.2% for patients ≥65 years vs. 69.7% for patients <65 years of age) or adverse events leading to treatment discontinuation (29.3% for patients ≥65 years vs. 18.8% for patients <65 years of age).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The pooled safety population in the WARNINGS AND PRECAUTIONS section reflects exposure to GAVRETO as a single agent at 400 mg orally once daily in 540 patients with *RET* altered solid tumours in ARROW. The safety of pralsetinib at a starting dose of 400 mg once daily was evaluated in 281 patients with locally advanced unresectable or metastatic NSCLC in ARROW.

The most common adverse reactions in patients with locally advanced unresectable or metastatic NSCLC in ARROW (≥25%) in GAVRETO-treated patients were anemia (56.2%), neutropenia (50.2%), aspartate aminotransferase (AST) increased (48.8%), constipation (44.5%), musculoskeletal pain (44.1%), fatigue (42%), hypertension (37.0%), alanine aminotransferase (ALT) increased (36.9%), edema (33.1%), leukopenia (38.1%), cough (30.6%) and pyrexia (28.8%).

Serious adverse reactions occurred in 40.2% of patients who received GAVRETO. The most common serious adverse reactions (≥ 2%) in GAVRETO-treated patients were pneumonia (17.1%), pneumonitis (6.8%), anemia (5.7%), hemorrhage (4.3%), pyrexia (2.8), urinary tract infection (2.5%), musculoskeletal pain (2.1%) and dyspnoea (2.1%). Fatal adverse reactions (Grade 5) occurred in 12 (4.3%) patients; fatal adverse reaction which occurred in >1 patient was pneumonia (n=8) and dyspnoea (n=2).

Dose reductions due to adverse reactions occurred in 46.3% of GAVRETO-treated patients. The most common adverse reactions (≥ 2%) resulting in dose reductions were neutropenia (16.4%), anemia (11.4%), pneumonitis (7.5%), lymphopenia (6.0%), blood creatine phosphokinase increased (5.7%), hypertension (5.0%), leukopenia (5.0%), fatigue (4.6%), pneumonia (3.9%) and thrombocytopenia (2.5%).

Permanent discontinuation of GAVRETO for adverse reactions occurred for 12.1% of patients. The most common adverse reactions (>1 patient) that led to permanent discontinuation of GAVRETO were pneumonitis (3.2%), pneumonia (2.8%), fatigue (1.1%), neutropenia (1.1%), anemia (<1%), dyspnoea (<1%) and thrombocytopenia (<1%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse reactions in real-world use.

The safety of GAVRETO in patients with locally advanced unresectable or metastatic NSCLC with a *RET* fusion was evaluated in ARROW, a multicenter, non-randomized, open-label, multi-cohort clinical trial [See 14 CLINICAL TRIALS]. Patients received GAVRETO at 400 mg orally once daily (n=281) for a median of 14.95 months (range: 0.3 to 44.3 months).

Adverse reactions that were reported in patients with locally advanced unresectable or metastatic NSCLC with a starting dose of 400 mg in the ARROW trial, regardless of investigator-assessed causality, are listed in Table 6.

Table 6: Adverse Reactions Reported in ≥10% of Patients with NSCLC Receiving GAVRETO in ARROW

Adverse Reactions	GAVRETO N=281	
	All Grades[1] n (%)	Grade 3-4 n (%)
Blood and Lymphatic System Disorders		
Anemia[2]	158 (56.2)	67 (23.8)
Leukopenia[3]	107 (38.1)	25 (8.9)
Lymphopenia[4]	59 (21.0)	37 (13.2)
Neutropenia[5]	141 (50.2)	65(23.1)
Thrombocytopenia[6]	60 (21.4)	17 (6.0)
Gastrointestinal Disorders		
Abdominal pain[7]	38 (13.5)	1 (<1)
Constipation	125 (44.5)	2(<1)
Diarrhea	84 (29.9)	7 (2.5)

Dry mouth	49 (17.4)	0
Nausea	53 (18.9)	0
Vomiting	39 (13.9)	3 (1.1%)
General Disorders and Administration Site Conditions		
Edema[8]	93 (33.1)	0
Fatigue[9]	118 (42.0)	7 (2.5)[20]
Pyrexia	81 (28.8)	2 (<1)
Hepatobiliary Disorders		
Alanine aminotransferase (ALT) increased	101 (35.9)	13 (4.6)
Aspartate aminotransferase (AST) increased	137(48.8)	18 (6.4)
Infections and Infestations		
Pneumonia[10]	67 (23.8)	37 (13.2)[21]
Urinary Tract Infection	45 (16.0)	10 (3.6)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[11]	124 (44.1)	7 (2.5)
Blood creatine phosphokinase increased	53 (18.9)	25 (8.9)
Nervous System Disorders		
Dizziness[12]	57 (20.3)	2 (<1)
Headache[13]	43 (15.3)	3 (1.1)
Taste Disorder[14]	47 (16.7)	0
Renal and Urinary Disorders		
Blood creatinine increased	70 (24.9)	2 (<1)
Respiratory Disorder		
Cough[15]	86 (30.6)	1 (<1)
Dyspnea	62 (22.1)	6 (2.1)[22]
Pneumonitis[16]	40 (14.2)	9 (3.2)
Skin and subcutaneous tissue disorders		
Rash[17]	49 (17.4)	0
Vascular Disorders		
Hemorrhage[18]	57(20.3)	10 (3.6)
Hypertension[19]	104 (37.0)	10 (3.6)

[1] Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

[2] Includes the preferred terms: Anaemia, Red blood cell count decreased, Aplastic anaemia, Haematocrit decreased, Haemoglobin decreased

[3] Includes the preferred terms: Leukopenia, White blood cell count decreased

[4] Includes the preferred terms: Lymphopenia, Lymphocyte count decreased

[5] Includes the preferred terms: Neutropenia, Neutrophil count decreased

[6] Includes the preferred terms: Thrombocytopenia, Platelet count decreased

[7] Includes the preferred terms: Abdominal pain, Abdominal pain upper

[8] Includes the preferred terms: Oedema, Swelling face, Peripheral swelling, Generalised oedema, Oedema peripheral, Face oedema, Periorbital oedema, Eyelid oedema, Swelling, Localised oedema

[9] Includes the preferred terms: Fatigue, Asthenia

[10] Includes the preferred terms: Pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia cytomegaloviral, Atypical pneumonia, Lung infection, Pneumonia bacterial, Pneumonia haemophilus, Pneumonia influenzal, Pneumonia streptococcal, Pneumonia Moraxella, Pneumonia staphylococcal, Pneumonia viral, Pneumonia Escherichia, Pneumonia pseudomonal, Atypical mycobacterial pneumonia, Candida pneumonia, Embolic pneumonia, Enterobacter pneumonia, Haemorrhagic pneumonia, Herpes simplex pneumonia, Miliary pneumonia, Paracancerous pneumonia, Parasitic pneumonia, Pneumonia acinetobacter, Pneumonia adenoviral, Pneumonia anthrax, Pneumonia blastomyces, Pneumonia bordetella, Pneumonia chlamydial, Pneumonia cryptococcal, Pneumonia escherichia,

Pneumonia fungal, Pneumonia helminthic, Pneumonia herpes viral, Pneumonia klebsiella, Pneumonia legionella, Pneumonia measles, Pneumonia mycoplasmal, Pneumonia necrotising, Pneumonia parainfluenzae viral, Pneumonia pneumococcal, Pneumonia proteus, Pneumonia respiratory syncytial viral, Pneumonia salmonella, Pneumonia serratia, Pneumonia toxoplasmal, Pneumonia tularaemia, Varicella zoster pneumonia

[11] Includes the preferred terms: Myalgia, Arthralgia, Pain in extremity, Neck pain, Musculoskeletal pain, Back pain, Musculoskeletal chest pain, Bone pain, Spinal pain, Musculoskeletal stiffness

[12] Includes the preferred terms: dizziness, dizziness postural and vertigo

[13] Includes the preferred terms: Headache, Tension Headache

[14] Includes the preferred terms: Dysgeusia, Ageusia

[15] Includes the preferred terms: Cough, Productive Cough

[16] Includes the preferred terms: Pneumonitis, Interstitial lung disease

[17] Includes the preferred terms: Rash, Rash maculo-papular, Dermatitis acneiform, Erythema, Rash generalised, Rash papular, Rash pustular, Rash macular, Rash erythematous

[18] Includes the preferred terms identified using the MedDRA 19.1 SMQ Haemorrhage (excl laboratory terms) narrow, with the exclusion of terms related invasive drug administration, terms related to rupture, disseminated intravascular coagulopathy, terms related to traumatic haemorrhages, and haemorrhagic terms related to pregnancy, birth or neonatal.

[19] Includes the preferred terms: Hypertension, Blood pressure increased

[20] Additionally, Grade 5 event was reported in 1 patient (0.4%)

[21] Additionally, Grade 5 events were reported in 8 patients (2.8%)

[22] Additionally, Grade 5 events were reported in two patients (0.7%)

8.3 Less Common Clinical Trial Adverse Reactions

Less Common Clinical Trial Adverse Reactions (occurring in ≥1% and <10% of NSCLC patients receiving GAVRETO in ARROW)

Blood and Lymphatic System Disorders: febrile neutropenia,

Ear and Labyrinth Disorders: vertigo

Eye Disorders: dry eye, vision blurred

Gastrointestinal Disorders: aphthous ulcer, colitis, gastroesophageal reflux disease, stomatitis

General Disorders and Administration Site Conditions: gait disturbance, fall

Infections and Infestations: sepsis

Musculoskeletal and Connective Tissue Disorders: muscle spasms, muscular weakness

Nervous System Disorders: balance disorder, peripheral neuropathy, peripheral sensory neuropathy

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings

Table 7 summarizes the laboratory abnormalities observed in ARROW in patients with NSCLC.

Table 7: Select Laboratory Abnormalities Worsening from Baseline Reported in ≥20% of Patients with NSCLC Receiving GAVRETO in ARROW

Laboratory Abnormality	GAVRETO N=281	
	All Grades* %	Grade 3 - 4* %
Chemistry		
Increased Aspartate Aminotransferase (AST)	80.4	3.2
Increased Alanine Aminotransferase (ALT)	58.7	3.9
Increased Alkaline Phosphatase (ALP)	43.4	2.5
Decreased Albumin	51.6	<1
Decreased Calcium Corrected	50.2	1.8
Decreased Phosphate	49.5	16.7
Increased Creatinine	44.5	1.4
Decreased Sodium	42.3	10.0
Increased Bilirubin	19.6	1.8
Hematology		
Decreased Neutrophils	69.8	21.0
Decreased Hemoglobin	78.6	17.8
Decreased Lymphocytes	73.3	31.7
Decreased Platelets	32.7	5.3
Decreased Leukocytes	79.0	11.4

** Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 except creatinine, which were graded per CTCAE version 5.0.*

Clinically relevant laboratory abnormalities < 20% of patients who received GAVRETO included increased phosphate (reported as hyperphosphatemia in 11.7% of patients).

8.5 Post-Market Adverse Reactions

Not applicable.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

GAVRETO should be avoided in patients with concomitant use of any of the following (see 4 DOSAGE AND ADMINISTRATION):

- strong CYP3A4 inhibitors,
- moderate CYP3A4 inhibitors,
- P-gp inhibitors,
- combined P-gp and strong CYP3A4 inhibitors
- combined P-gp and moderate CYP3A4 inhibitors,
- strong CYP3A4 inducers,
- moderate CYP3A4 inducers.

9.2 Drug Interactions Overview

CYP3A4 and/or P-gp Inhibitors

Strong CYP3A4 Inhibitors: Coadministration of multiple doses of voriconazole is predicted to increase the pralsetinib AUC by 122% and C_{max} by 20%.

Moderate CYP3A4 Inhibitors: Coadministration of multiple doses of fluconazole is predicted to increase the pralsetinib AUC by 71% and C_{max} by 15%.

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

Combined P-gp Inhibitors and Moderate CYP3A4 Inhibitors: Coadministration of multiple doses of diltiazem or verapamil is predicted to increase the pralsetinib AUC by 84-108% and C_{max} by 60-68%.

Combined P-gp Inhibitors and Strong CYP3A4 Inhibitors: Coadministration of a single dose of pralsetinib 200 mg on Day 4 with itraconazole (200 mg twice daily on Day 1 followed by 200 mg once daily for 13 days), in healthy subjects, increased pralsetinib $AUC_{0\text{-}inf}$ by 251% and C_{max} by 84%, compared to a 200 mg dose of pralsetinib administered alone.

CYP3A4 Inducers

Strong CYP3A4 Inducers: Coadministration of pralsetinib 400 mg as a single dose on Day 9 with rifampin 600 mg once daily for 16 days, in healthy subjects, decreased pralsetinib $AUC_{0\text{-}inf}$ by 68% and C_{max} by 30%, relative to a 400 mg dose of pralsetinib administered alone.

Moderate CYP3A4 Inducers: Coadministration of multiple doses of efavirenz or phenobarbital is predicted to decrease the pralsetinib AUC by 32-45% and C_{max} by 14-18%.

Mild CYP3A4 Inducers: Based on a population PK analysis, CYP3A4 mild inducers decreased pralsetinib exposures, but were not clinically significant in patients with NSCLC.

No clinically significant differences in the pharmacokinetics of pralsetinib were identified when co-administered with gastric acid reducing agents, compared to GAVRETO administered alone.

In vitro studies indicate that pralsetinib is a time-dependent inhibitor of Cytochrome P450 enzymes [CYP]3A4/5 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. 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.

9.3 Drug-Behavioural Interactions

Behavioural interactions have not been established.

9.4 Drug-Drug Interactions

The drugs listed in Table 8 are based on clinical studies.

Table 8: Established or Potential Drug-Drug Interactions

Proper / Common name	Source of Evidence	Effect	Clinical comment
Strong CYP3A4 Inhibitors (e.g. voriconaxole)	PBPK Modeling	Coadministration of pralsetinib with a strong CYP3A4 inhibitor increased plasma pralsetinib concentrations. This may increase the risk of adverse reactions.	• Avoid coadministration with a strong CYP3A4 inhibitor. • If coadministration with a strong CYP3A4 inhibitor cannot be avoided, reduce the dose of GAVRETO (see 4.2 Recommended Dose and Dosage Adjustment).
Moderate CYP3A4 Inhibitors (e.g. fluconazole)	PBPK Modeling	Coadministration of pralsetinib with a moderate CYP3A4 inhibitor increased plasma pralsetinib concentrations. This may increase the risk of adverse reactions.	• Avoid coadministration with a moderate CYP3A4 inhibitor. • If coadministration with a moderate CYP3A4 inhibitor cannot be avoided, reduce the dose of GAVRETO (see 4.2 Recommended Dose and Dosage Adjustment).

Proper / Common name	Source of Evidence	Effect	Clinical comment
P-gp Inhibitors (e.g. cyclosporine)	Clinical Trial	Coadministration of pralsetinib with a P-gp inhibitor increased plasma pralsetinib concentrations. This may increase the risk of adverse reactions.	• Avoid coadministration with a P-gp inhibitor. • If coadministration with a P-gp inhibitor cannot be avoided, reduce the dose of GAVRETO (see 4.2 Recommended Dose and Dosage Adjustment).
Combined P-gp and Moderate CYP3A4 Inhibitor (e.g., diliazem, verapamil)	PBPK Modeling	Coadministration of pralsetinib with a combined P-gp and moderate CYP3A4 inhibitor increased plasma pralsetinib concentrations. This may increase the risk of adverse reactions.	• Avoid coadministration with a combined P-gp and moderate CYP3A4 inhibitor. • If coadministration with a combined P-gp and moderate CYP3A4 inhibitor cannot be avoided, reduce the dose of GAVRETO (see 4.2 Recommended Dose and Dosage Adjustment).
Combined P-gp and Strong CYP3A4 Inhibitor (e.g., itraconazole)	Clinical Trial	Coadministration of pralsetinib with a combined P-gp and strong CYP3A4 inhibitor increased plasma pralsetinib concentrations. This may increase the risk of adverse reactions.	• Avoid coadministration with a combined P-gp and strong CYP3A4 inhibitor. • If coadministration with a combined P-gp and strong CYP3A4 inhibitor cannot be avoided, reduce the dose of GAVRETO (see 4.2 Recommended Dose and Dosage Adjustment).
Strong CYP3A4 Inducers (e.g. rifampin)	Clinical Trial	Coadministration of pralsetinib with a strong CYP3A4 inducer decreased plasma pralsetinib concentrations. This may result in decreased efficacy of pralsetinib.	• Avoid coadministration with a strong CYP3A4 inducer. • If coadministration with a strong CYP3A4 inducer cannot be avoided, increase the dose of GAVRETO (see 4.2 Recommended Dose and Dosage Adjustment).
Moderate CYP3A4 Inducers (e.g. efavirenz, phenobarbital)	PBPK Modeling	Coadministration of pralsetinib with a moderate CYP3A4 inducer decreased plasma pralsetinib concentrations. This may result in decreased efficacy of pralsetinib.	• Avoid coadministration with a moderate CYP3A4 inducer. • If coadministration with a moderate CYP3A4 inducer cannot be avoided, increase the dose of GAVRETO (see 4.2 Recommended Dose and Dosage Adjustment).

PBPK= physiological based pharmacokinetic

9.5 Drug-Food Interactions

GAVRETO is to be taken on an empty stomach (no food intake for at least 2 hours before and at least 1 hour after taking GAVRETO). 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) $AUC_{0\text{-}INF}$ was increased by 122% (96% - 152%), and the median T_{max} was delayed from 4 to 8.5 hours, compared to the fasted state [see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY].

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

NOC/c 10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

GAVRETO is a tyrosine kinase inhibitor that targets oncogenic *RET* fusions and mutations, including V804 gatekeeper mutations associated with resistance to other therapies. In vitro, GAVRETO inhibited several oncogenic *RET* fusions and mutations (CCDC6-RET, RET V804L, RET V804M and RET M918T) with half maximal inhibitory concentrations (IC_{50}) less than 0.5 nM. In a broad panel of purified enzyme assays, GAVRETO inhibited DDR1, TRKC, FLT3, JAK1-2, TRKA, VEGFR2, PDGFRB, and FGFR1 at higher concentrations that were still clinically achievable at Cmax, with 81-fold selectivity for *RET* over VEGFR2.

RET fusion proteins and activating point mutations can drive tumorigenic potential through hyperactivation of downstream signaling pathways leading to uncontrolled cell proliferation. GAVRETO exhibited anti-tumor activity in cultured cells and animal tumor implantation models representing multiple tumor types harboring oncogenic *RET* fusions or mutations (*KIF5B-RET, CCDC6-RET, RET M918T, RET C634W*, as well as the *V804L* and *V804M* mutants associated with cabozantinib and vandetanib resistance).

GAVRETO was 14-, 40-, and 12-fold more potent on *RET* in a cellular setting compared with representatives of the VEGFR2, FGFR, or JAK families, respectively.

GAVRETO demonstrated prolonged survival in intracranial mouse models of *KIF5B-RET* and *CCDC-6 RET* compared with vehicle controls. Antitumor activity correlated with GAVRETO exposures and pharmacodynamic modulation of tumor biomarkers, including direct inhibition of *RET* kinase activity.

10.2 Pharmacodynamics

Exposure-Response Relationships

Based on the data from ARROW, exposure-response relationships for any Grade 3 or 4 adverse reaction were observed at higher exposures, with a faster time to onset for adverse reactions with increasing pralsetinib exposure.

10.3 Pharmacokinetics

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) in patients. Dose proportionality could not be established for the 200-400 mg QD dose range in patients due to the low number of patients receiving doses outside the 400 mg QD dosing regimen. However, following a single dose in healthy volunteers, pralsetinib was found to be dose proportional across the 200-400 mg dose range.

Table 9: Summary of Pralsetinib Pharmacokinetic Parameters in Patients with NSCLC Receiving GAVRETO in ARROW

	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	$AUC_{0-\infty}$ (ng•h/mL)	CL/F (L/h)	V_z/F (L)
Single dose (n=87)	1610	4.00	14.7	33,800	11.8	228
Repeat dose, Steady state (n=77)	2830	4.00	22.2	43,900 [a]	9.10	268

[a] *AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours post-dose;*
$AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 to infinity;
CL/F = apparent oral clearance, unadjusted for bioavailability; C_{max} = maximum plasma concentration; T_{max} = time of maximum plasma concentration; $t_{1/2}$ = apparent elimination half-life; V_z/F = apparent volume of distribution during the terminal phase, unadjusted for bioavailability.
Note: Pharmacokinetic parameters are described for single-dose (Cycle 1 Day 1) and at steady-state (Cycle 1 Day 15) at the recommended dosage of 400 mg once daily.
Values provided are geometric mean except for T_{max} (median) and $t_{1/2}$ (arithmetic mean).

Absorption

The median time to peak concentration (T_{max}) ranged from 2.0 to 4.0 hours following single doses of pralsetinib 60 mg to 600 mg (0.15 to 1.5 times the approved recommended dose). The C_{max} of pralsetinib was increased by 104% and the $AUC_{0-\infty}$ was increased by 122% when GAVRETO was taken with a high-calorie, high-fat meal compared to those in the fasted state.

Distribution:

The mean apparent volume of distribution of pralsetinib is 228 L. In vitro protein binding of pralsetinib is 97.1% and is independent of concentration. The blood-to-plasma ratio is 0.6 to 0.7.

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, unchanged pralsetinib was the predominant radioactive component in plasma, urine, and feces, while its metabolites from oxidation (M531, M453, M549b) and glucuronidation (M709) were detected in small to trace amounts (~5%).

Elimination

The mean plasma elimination half-life of pralsetinib was 14.7 hours following single doses of pralsetinib 400 mg (the recommended dose), and steady state exposures are estimated to be reached by 3 to 5 days. The steady state mean apparent oral clearance of pralsetinib is 9.1 L/h.

Following a single oral dose of radiolabeled pralsetinib to healthy subjects, 72.5% of the radioactive dose was recovered in feces and 6.1% in urine.

Special Populations and Conditions

- ***Geriatrics:*** No clinically significant differences in the pharmacokinetics of pralsetinib were observed based on age (18 to 90 years).
- ***Sex:*** No clinically significant differences in the pharmacokinetics of pralsetinib were observed based on sex.
- ***Ethnic origin:*** No clinically significant differences in the pharmacokinetics of pralsetinib were observed based on race (White, Black, or Asian).
- ***Hepatic Insufficiency:*** No clinically significant differences in the pharmacokinetics of pralsetinib were observed based on mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin >1 to 1.5 times ULN and any AST).

  In a dedicated hepatic impairment trial, following a single oral dose of 200 mg pralsetinib, peak pralsetinib exposure was similar in subjects with moderate hepatic impairment (as defined by Child-Pugh criteria) compared to subjects with normal hepatic function, with geometric mean ratios (GMR) (90% CI) of 98.6% (59.7, 163) for C_{max} and 112% (65.4, 193) for $AUC_{0-\infty}$. In subjects with severe hepatic impairment (as defined by ChildPugh criteria), $AUC_{0-\infty}$ was also similar compared to subjects with normal hepatic function (85.8% [51.1, 144]). C_{max} was slightly lower in subjects with severe hepatic impairment compared to subjects with normal hepatic function, with a C_{max} GMR of 67.9% (35.3, 131). Unbound C_{max} ($C_{max,u}$) and $AUC_{0-\infty}$ ($AUC_{0-\infty,u}$) were slightly higher in subjects with severe hepatic impairment (as defined by Child-Pugh criteria) compared to subjects with normal hepatic function, with a $C_{max,u}$ GMR of 129% (70.4, 236) and $AUC_{0-\infty,u}$ GMR of 163% (98.7, 268). Similar PK results were obtained when hepatic impairment subjects were classified by NCI-ODWG criteria.

  Therefore, no dose adjustment is needed in patients with hepatic impairment.
- ***Renal Insufficiency:*** No clinically significant differences in the pharmacokinetics of pralsetinib were observed based on mild to moderate renal impairment (CL_{CR} 30 to 89 mL/min estimated by Cockcroft-Gault). The effect of severe renal impairment (CL_{CR} 15 to 29 mL/min) or end-stage renal disease (CL_{CR} <15 mL/min) on the pharmacokinetics of pralsetinib is unknown.
- ***Obesity:*** No clinically significant differences in the pharmacokinetics of pralsetinib were observed based on body weight (39.5 to 156.3 kg).

11 STORAGE, STABILITY AND DISPOSAL

Store 15-30°C in original bottle. Protect from moisture. Keep out of the sight and reach of children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

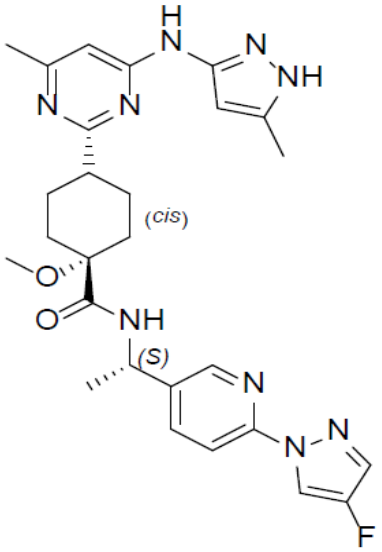
12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common name:	Pralsetinib
Chemical name:	(cis)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridine-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-yl)cyclohexanecarboxamide
Molecular formula and molecular mass :	C27H32FN9O2 / and 533.61 g/mol
Structural formula:	

Physicochemical properties:

Description:	White to off white to yellow solid.
Solubility:	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.

14 CLINICAL TRIALS

NOC/c

14.1 Clinical Trials by Indication

Locally Advanced Unresectable or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Table 10: Summary of Patient Demographics for the Evaluation of Efficacy in the *RET* fusion-positive Locally Advanced Unresectable or Metastatic NSCLC*(ARROW)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
BLU-667-1101 (ARROW)	Multicenter, non-randomized, open-label, multi-cohort trial	400 mg GAVRETO, oral, treatment for at least 1 cycle (28 days)	130 (patients previously treated with platinum-based chemotherapy) 107 (treatment naïve patients)	60 years (26 to 85 years) 62 years (30 to 87 years)	64 male/ 66 female 50 male/ 57 female

**with measurable disease at baseline*

The efficacy of GAVRETO was demonstrated in patients with *RET* fusion-positive locally advanced unresectable or metastatic NSCLC in ARROW, a multicenter, non-randomized, open-label, multi-cohort clinical trial (NCT03037385). All NSCLC patients were required to have locally advanced unresectable or metastatic disease with measurable disease by Response Evaluable Criteria in Solid Tumors (RECIST) version 1.1. (v1.1) and have a *RET* fusion as determined by local testing (74.4% next generation sequencing [NGS] [48.0% tumor sample, 12.8% plasma, 13.6% unknown], 24.0% fluorescence in situ hybridization [FISH] testing of tumour tissue, 1.6% other). 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. The major efficacy outcome measures were overall response rate (ORR) according to RECIST v1.1 and duration of response (DOR) as evaluated by a Blinded Independent Central Review (BICR).

NSCLC Previously Treated with Platinum Chemotherapy

The assessment of efficacy was based on a total of 130 patients with *RET* fusion-positive locally advanced unresectable or metastatic NSCLC previously treated with platinum-based chemotherapy who received GAVRETO at a starting dose of 400 mg orally once daily.

The demographic characteristics across the 130 patients were: 50.8% female, 40.0% White, 50% Asian, 4.6% Hispanic/Latino, and the median age was 59.0 years (range 26 to 85 years) with 34.6% ≥65 years of age. The majority of patients had an ECOG performance status at baseline of 0-1 (95.4%) or 2 (3.8%).

The patient population was composed of those with metastatic (99.2%) or locally advanced unresectable (<1%) disease. The predominant histology was adenocarcinoma (96.2%).

Forty-point-eight percent of patients had either a history of or current CNS metastases. The most common *RET* fusion partners were *KIF5B* (70.0%) and *CCD6* (19.2%). The extent of prior systemic therapy is described in Table 11.

Table 11: Prior Systemic Therapy *RET* fusion-positive Locally Advanced Unresectable or Metastatic NSCLC (ARROW)

Extent of Prior Systemic Therapy	% of Patients
Prior platinum-based chemotherapy	100%
Prior PD-1/PD-L1 inhibitor	41.5%
Prior Multikinase Inhibitors	26.9%
Other systemic therapies	31.5%

Treatment-naïve *RET* fusion-positive NSCLC

Efficacy was evaluated in 107 patients with treatment-naïve *RET* fusion-positive NSCLC enrolled into ARROW who received GAVRETO at a starting dose of 400 mg orally once daily. Per protocol, based on investigator assessment, all patients were deemed not eligible for platinum-based chemotherapy.

The demographic characteristics across the 107 patients were: 53.3% female, 48.6% White, 44.9% Asian, and the median age was 62.0 years (range 30 to 87 years) with 40.2% ≥65 years of age. The majority of patients had an ECOG performance status at baseline of 0 (30.8%) or 1 (68.2%).

All patients had metastatic disease and adenocarcinoma histology. Twenty-eight percent of patients had a history of or current brain metastases. The most common *RET* fusion partners were *KIF5B* (71.0%) and *CCD6* (17.8%).

Study results in patients with NSCLC Previously Treated with Platinum Chemotherapy

Efficacy results are summarized in Table 12. The median time to first response was 1.84 months (range: 1.3 to 11.4 months) and the median follow-up time for duration of response was 29.3 months.

Table 12: Efficacy Results for ARROW (*RET* fusion-positive Locally Advanced Unresectable or Metastatic NSCLC Previously Treated with Platinum Chemotherapy)

Efficacy Parameter	GAVRETO (N=130)
Overall Response Rate (ORR)[a] (95% CI)	63.1% (54.2%, 71.4%)
Complete Response (%)	6.2%
Partial Response (%)	56.9%
Duration of Response (DOR)	**(N=82)**
DOR, median (95% CI) in months	38.8 (14.8, 40.4)
% DOR ≥6 months	80.5%

CI = confidence interval

[a] Confirmed overall response rate assessed by Blinded Independent Central Review (BICR).

Exploratory Results

Prior anti-PD-1 or anti-PD-L1 therapy

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 59.3% (95% CI: 45.0, 72.4) and the median DOR (N=32) was 22.3 months (95% CI: 8.0, NR).

Brain metastases

The RECIST CNS ORR assessed by BICR was 7 out of 10 response evaluable patients with brain metastases at baseline, including 2 patients with a CNS complete response. No patients without history

of CNS involvement and receiving a starting dose of 400 mg once daily developed new CNS metastases on study.

Study results in patients with treatment-naïve *RET* fusion-positive NSCLC

Efficacy results are summarized in Table 13. The median time to first response was 1.84 months (range: 0.9 to 6.1 months) and the median follow-up time for duration of response was 20.2 months.

Table 13: Efficacy Results for ARROW (Treatment-Naïve *RET* fusion-positive Locally Advanced Unresectable or Metastatic NSCLC)

Efficacy Parameter	**GAVRETO (N=107)**
Overall Response Rate (ORR)[a] (95% CI)	77.6% (68.5%, 85.1%)
Complete Response (%)	6.5%
Partial Response (%)	71.0%
Duration of Response (DOR)	**(N=83)**
DOR, median (95% CI) in months	13.4 (9.4, 23.1)
% DOR ≥6 months	74.7%

CI = confidence interval

[a] Confirmed overall response rate assessed by Blinded Independent Central Review (BICR).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

In the 4- and 13-week repeat-dose toxicity studies conducted in Sprague Dawley rats and Cynomolgus monkeys administered pralsetinib via once daily oral dosing dose levels tested ranged from 20-75 mg/kg/day and 5-20 mg/kg/day, respectively, in rats; and, 2.5-40 mg/kg/day and 2-10 mg/kg/day, respectively, in Cynomolgus monkeys. In the 13-week repeat-dose toxicity studies, target organs in the rat included the bone marrow, with findings of decreased cellularity histopathologically consistent with decreases in red blood cells (RBCs) and mild decreases in white blood cells (WBCs), kidney (decreased weight and tubular basophilia/mineralization), and lung (macrophage aggregation).

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 ≥2.6 times and ≥1.1 times, respectively, the human exposure based on AUC at the clinical dose of 400 mg. In monkeys, necrosis and hemorrhage were multiorganic (attributed to sepsis with intralesional bacteria in lymph nodes, spleen, heart and kidneys).

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.

Bone (increased physeal thickness in the sternum and femur) and teeth (incisor fractures and histologic dentin matrix alteration, ameloblast/odontoblast degeneration, mixed cell inflammation, odontoblast necrosis) findings were present in rats and may be related to VEGFR/FGFR inhibition. Although similar toxicities were not seen in the 13-week monkey study, treatment with 15/7.5 mg/kg pralsetinib in the 28-day study resulted in physeal dysplasia in the femur of monkeys at doses results in exposures similar

to the human exposure (AUC) at the clinical dose of 400 mg. Recovery was not assessed in the 13-week studies, but increased physeal thickness in the femur and incisor degeneration did not show evidence of complete recovery within the 14-day period recovery time in the 28-day rat study.

Additional findings at approximately 2x exposure margins in the rat included degenerative changes in male and female reproductive organs. Increased blood pressure was observed in rats after a single dose of 25 mg/kg (2x margin). Regarding local exposure and toxicity, there was no evidence of gastrointestinal disturbance in either species up to a dose of 10 mg/kg. At higher doses in monkeys, gastrointestinal effects including mucosal ulcerations and hemorrhage with subsequent fatal secondary bacterial sepsis were observed.

Carcinogenicity

Carcinogenicity studies with pralsetinib have not been conducted.

Genotoxicity

Pralsetinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay with or without metabolic activation. Pralsetinib was also negative in both in vitro and in vivo micronucleus tests.

Reproductive and Developmental Toxicology

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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrGAVRETO®
pralsetinib capsules

Read this carefully before you start taking **GAVRETO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **GAVRETO.**

Serious Warnings and Precautions

- GAVRETO should only be prescribed by doctors who are experienced in the use of drugs to treat cancer.
- GAVRETO may harm your unborn baby.
- Wounds may not heal well during treatment with GAVRETO. GAVRETO should not be taken for at least 5 days before surgery and for at least 14 days after surgery and until the wound is fully healed.

GAVRETO may cause the following serious side effects:

- **Lung problems: Interstitial lung disease/Pneumonitis** (inflammation of lungs) can occur while taking GAVRETO. They may cause death.
- **Hypertension** (high blood pressure): Treatment with GAVRETO can cause high blood pressure. Your healthcare professional will ensure your blood pressure is normal before treatment. They will monitor your blood pressure levels after one week of treatment and at least monthly after. They might give you medicine to treat your high blood pressure.
- **Liver problems:** Treatment with GAVRETO can cause liver problems like **increased levels of liver enzymes (ALT, AST) in the blood**. You will have regular blood tests done before starting your treatment and then every two weeks during the first three months, then monthly after, while you are taking GAVRETO. These blood tests will tell your healthcare professional how your liver is working.
- **Hemorrhage** (bleeding problems): Treatment with GAVRETO can cause bleeding problems. These bleeding problems can cause death.

See the Serious side effects and what to do about them table, below, for more information on these serious side effects.

What is GAVRETO used for?

Please see the boxed text below.

For the following indication GAVRETO has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

GAVRETO is used to treat adults with a type of lung cancer called non-small cell lung cancer (NSCLC). The non-small cell lung cancer:

- Is caused by abnormal Rearranged During Transfection (*RET*) gene(s) and
- Cannot be removed by surgery or has spread to other parts of the body.

A test will be done to determine if the non-small cell lung cancer is caused by *RET* genes.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does GAVRETO work?

GAVRETO is a type of drug that targets and blocks abnormal *RET* genes. These *RET* genes encourage cancer cells to grow. GAVRETO might help slow down the growth or spread of cancer tumour cells.

What are the ingredients in GAVRETO?

Medicinal ingredients: pralsetinib

Non-medicinal ingredients: citric acid, FD&C blue #1 (Brilliant Blue FCF), hydroxypropyl methylcellulose (HPMC, hypromellose), magnesium stearate, microcrystalline cellulose (MCC), pharmaceutical grade printing ink, pregelatinized starch, sodium bicarbonate, and titanium dioxide.

GAVRETO comes in the following dosage forms:

- Capsules, 100mg pralsetinib

Do not use GAVRETO if:

- You are allergic to pralsetinib or any of the other ingredients in GAVRETO or the bottle.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take GAVRETO. Talk about any health conditions or problems you may have, including if you:

- Have a history of lung or breathing problems other than lung cancer.
- Have or had high blood pressure.
- Have or had liver problems.
- Are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed.
- Are younger than 18 years of age.
- Are 65 years or older. This is because you maybe more likely to experience side effects. These side effects can be serious.
- Had or plan to have surgery.

Other warnings you should know about:

Pregnancy and breastfeeding:

Female patients

- If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your healthcare professional.
- You should not take GAVRETO if you are pregnant. It may harm your unborn baby.
- If you are able to become pregnant:
  - Your healthcare professional will do a pregnancy test before you start taking GAVRETO. This test must show that you are not pregnant.
  - Avoid becoming pregnant while you are taking GAVRETO.
  - Use effective birth control during your treatment and for at least 2 weeks after your last dose. The birth control methods you use must not contain hormones. Hormonal birth control methods (like birth control pills) might not work with GAVRETO. Ask your healthcare professional about methods of birth control available to you.
  - Tell your healthcare professional right away if you become pregnant or think you may be pregnant during your treatment with GAVRETO.
- Do not breastfeed while you are taking GAVRETO and for at least one week after your last dose.

Male patients

- If your sexual partner can get pregnant, use highly effective birth control, including a barrier method (such as a condom) while you are on GAVRETO and for at least 1 week after your last dose.

Fertility in female and male patients:

- GAVRETO may affect your fertility. Talk to your healthcare professional if this is a concern for you.

Driving and using machines:

- Before you do tasks that require special attention, wait until you know how you respond to GAVRETO.

Check-ups and testing: You will have regular visits with your healthcare professional during your treatment. These visits might include the following to monitor your health:

- physical exams with a blood pressure check
- blood tests
- diagnostic imaging like a CT scan

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

The following may interact with GAVRETO:

- Medicines for fungal infections such as voriconazole, fluconazole, itraconazole and ketoconazole.
- Medicines for bacterial infections such as rifampin and clarithromycin.
- Medicines for HIV infection such as efavirenz, indinavir and ritonavir.
- A medicine to suppress the body's immune system called cyclosporine.
- Medicines used to treat blood pressure such as diltiazem and verapamil.
- A medicine for seizures called phenobarbital.

How to take GAVRETO:

- Take GAVRETO exactly as your healthcare professional tells you to.
- 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 professional tells you to.
- Your healthcare professional will monitor your health. They may interrupt, reduce or stop your dose. This may occur based on your current health, if you take certain other medications or if you have certain side effects.

Usual dose:

Adults:

- Take 400 mg (four 100 mg tablets) once daily by mouth.
- Your healthcare professional will monitor your health. They may interrupt, reduce or stop your dose. This may occur based on your current health, if you take certain other medications or if you have certain side effects.

Overdose:

If you think you, or a person you are caring for, have taken too much GAVRETO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If a dose of GAVRETO is missed:

- Take the missed dose as soon as you remember on the same day. Take the next dose at your regular time on the next day.
- If you do not remember on the same day, do not take an extra dose the next day.
- If you vomit after taking a dose of GAVRETO, do not take another dose on that same day. Take your next dose at your regular time on the next day.

What are possible side effects from using GAVRETO?

These are not all the possible side effects you may have when taking GAVRETO. If you experience any side effects not listed here, tell your healthcare professional.

- Constipation
- Diarrhea
- Dry mouth
- Bleeding from your nose, gums, vagina
- Change in taste
- Cough
- Fever
- Headache
- Dizziness
- Dry eyes, blurred vision
- Tiredness
- Stomach pain
- Pain in your muscles, joints, neck, bones, nerves, chest, back, arms and/or legs
- Muscle weakness and spasms
- Nausea, vomiting
- Swelling: eyelids, face, hands, feet
- Bruising
- Rash

Your healthcare professional will do some tests before, during and after your treatment. These include blood tests to check your blood cell count and liver health. More frequent tests might be needed. They will tell you if your test results are abnormal and if you need treatment.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness		✓	
Hypertension (high blood pressure): shortness of breath, fatigue, headaches, vision problems, confusion, dizziness or fainting, nosebleeds, chest pain or pressure, and/or swelling in your ankles and legs; OR sometimes there are no symptoms.		✓	
Liver problems (Increased levels of liver enzymes (ALT, AST) in the		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
blood): dark urine, fatigue, loss of appetite, nausea or vomiting, sleepiness, bleeding or bruising, yellowing of the skin or eyes, pain on the upper right side of the stomach area			
Leukopenia, Lymphopenia, Neutropenia (decreased white blood cells): infections, fatigue, fever, aches, pains and flu-like symptoms		✓	
Pneumonia (infection in the lungs): chest pain when you breath or cough, confusion, cough which may produce phlegm, fatigue, fever, sweating and shaking chills, nausea, vomiting or diarrhea, shortness of breath		✓	
Interstitial Lung Disease (ILD) / Pneumonitis (inflammation of the lung tissue): shortness of breath, cough, fatigue, loss of appetite, unintentional weight loss			✓
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		✓	
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder and urethra): Pain or burning sensation while urinating, frequent urination, blood or pus in urine, pain in the pelvis or lower back, strong or foul smelling urine, cloudy urine, fever or chills, nausea or vomiting.		✓	
COMMON			
Hemorrhage (bleeding problems): unusual bleeding or bruising of the skin, pink or brown urine, blood in urine, menstrual bleeding that is heavier than normal, unusual		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
vaginal bleeding, frequent nosebleeds			
Colitis (bowel inflammation): severe or persistent diarrhea, abdominal pain, nausea and vomiting, fever		✓	
Gastrointestinal (GI) bleeding (bleeding anywhere along the GI tract between mouth and anus): (bleeding in esophagus, stomach or first part of small intestines): blood in vomit or vomit looks like coffee-grounds, black tarry stool, bright red blood in your stool or coming from rectum, rapid pulse, low blood pressure, low urine flow, confusion, weakness, dizziness; (bleeding from large intestine, rectum): bright red blood in your stool or coming from rectum, rapid pulse, low blood pressure, low urine flow, confusion, weakness, dizziness			✓
Hemoptysis: coughing up blood or blood clots		✓	
Intracerebral, Intracranial hemorrhage (bleeding in the brain/skull): sudden, severe headache; confusion; drowsiness or difficulty being awakened; change in speech; nausea and vomiting; seizures; loss of consciousness			✓
Nervous system disorders: difficulty walking, trouble with balance, falls, dizziness, light headedness, double vision, nausea, weakness, numbness or paralysis of limbs or face, difficulty speaking, severe headache, difficulty seeing, loss of consciousness, confusion,		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
disorientation			
Pancytopenia (decreased red and white blood cells and platelets): low red blood cell count: paleness of the skin, fatigue, rapid heart rate, shortness of breath; low white blood cell count: fever, and symptoms of infection such as cough; low platelet count: bruising easily and heavy bleeding		✓	
Sepsis (Infection of the blood): fever or dizziness, chills, high or very low body temperature, little or no urine, low blood pressure, palpitations, rapid breathing, rapid heartbeat.			✓
Stomatitis (inflammation and ulceration of the mouth and lips): painful, red, shiny or swollen gums, tongue, mouth or throat sores, blood in the mouth, difficult or painful swallowing or talking, dry mouth, mild burning, or pain when eating food		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store 15-30°C in original bottle.
- Protect from moisture.
- Keep out of reach and sight of children.
- Ask your pharmacist how to throw away drugs you no longer use.

If you want more information about GAVRETO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.rochecanada.com, or by calling 1-888-762-4388.

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