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CAP-GAV-2023 04

# Gavreto™

Pralsetinib

## 1. DESCRIPTION

### 1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Pharmacotherapeutic group: Antineoplastic agent, protein kinase inhibitors

ATC code: L01EX23

### 1.2 TYPE OF DOSAGE FORM

Hard Capsule

Gavreto 100mg are size 0 light blue opaque HPMC capsules, printed in white ink with “BLU-667” on the capsule shell body and “100mg” on the capsule shell cap, containing white to off white powder.

### 1.3 ROUTE OF ADMINISTRATION

Oral

### 1.4 STERILE / RADIOACTIVE STATEMENT

Not applicable

### 1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

*Active ingredient(s):* pralsetinib

*Excipients:*

*Capsule content: hydroxypropyl methylcellulose, microcrystalline cellulose, sodium bicarbonate, citric acid, anhydrous, magnesium stearate, pregelatinized starch.*

*Capsule shell: hypromellose, titanium dioxide, FD&C Blue #1 (Brilliant Blue FCF)*

*Printing ink:* shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, purified water, potassium hydroxide, and titanium dioxide.

## 2. CLINICAL PARTICULARS

### 2.1 THERAPEUTIC INDICATION(S)

***Non-Small Cell Lung Cancer (NSCLC)***

Gavreto is indicated for the treatment of adult patients with rearranged during transfection (*RET*) fusion-positive, locally advanced or metastatic NSCLC.

***RET-Mutant Medullary Thyroid Cancer (MTC)***

Gavreto is indicated for the treatment of adult patients with locally advanced or metastatic *RET*-mutant MTC who require systemic therapy.

### 2.2 DOSAGE AND ADMINISTRATION

***General***

A validated assay is required for the selection of patients with a *RET*-gene fusion (NSCLC) or a *RET*-gene mutation (MTC).

***Dosage***

Gavreto hard capsules should be taken on an empty stomach. Do not to eat for at least 2 hours before and at least 1 hour after taking Gavreto.

Gavreto hard capsules should be swallowed whole with a glass of water and must not be opened or chewed.

***Adults***

The recommended dose of Gavreto for adults is 400 mg given orally, once daily.

***Duration of Treatment***

It is recommended that patients are treated with Gavreto until disease progression or unmanageable toxicity.

***Delayed or Missed Doses***

If a planned dose of Gavreto is missed, patients can make up that dose unless the next dose is due within 12 hours. Resume the regular daily dose schedule for Gavreto the next day.

If vomiting occurs after taking a dose of Gavreto, patients should take the next dose at the scheduled time.

## Dose Modifications

*Adverse Reactions*

Management of adverse reactions may require temporary interruption, dose reduction, or discontinuation of treatment with Gavreto, based on the prescriber's assessment of the patient's safety or tolerability.

Table 1 provides recommended dose reduction advice. Recommendations for dose modifications for the management of specific adverse reactions are provided in Table 2. Gavreto treatment should be permanently discontinued if a patient is unable to tolerate the 100 mg once daily dose.

**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 |

**Table 2: Recommended Dose Modifications for Adverse Reactions**

| Adverse Reaction | Severity* | Dosage Modification |
|---|---|---|
| **Pneumonitis/Interstitial Lung Disease (ILD)** | Grade 1 or 2 | Withhold Gavreto until resolution. Resume at a reduced dose as shown in Table 1.<br>Permanently discontinue Gavreto for recurrent ILD/pneumonitis. |
| | Grade 3 or 4 | Discontinue Gavreto. |
| **Hypertension** | Grade 3 | Withhold Gavreto for Grade 3 hypertension that persists despite optimal antihypertensive therapy.<br>Resume at a reduced dose as shown in Table 1 when hypertension is controlled. |
| | Grade 4 | Discontinue Gavreto. |

**Table 2: Recommended Dose Modifications for Adverse Reactions**

| Adverse Reaction | Severity* | Dosage Modification |
|---|---|---|
| **Hepatic Transaminase Elevations** | Grade 3 or 4 | Withhold Gavreto and monitor AST/ALT once weekly until resolution to Grade 1 or baseline.<br>Resume at a reduced dose as shown in Table 1.<br>For recurrent events at Grade 3 or higher, discontinue Gavreto. |
| **Hemorrhagic Events** | Grade 3 or 4 | Withhold GAVRETO until resolution to Grade 1.<br>Resume at a reduced dose as shown in Table 1.<br>Discontinue GAVRETO for life-threatening or recurrent severe hemorrhagic events. |
| **QT Prolongation** | Grade 3 | Interrupt treatment with Gavreto for QTc intervals >500 ms until QTc interval returns to <470 ms.<br>Resume at the same dose if risk factors that cause QT prolongation are identified and corrected.<br>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 Adverse Reactions** | Grade 3 or 4 | Withhold Gavreto until improvement to ≤ Grade 2. Resume at a reduced dose as shown in Table 1.<br>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

### *Interactions with other Medicinal Products*

*Dose modification for use with strong cytochrome P-450 (CYP)3A4 inhibitors or combined P-glycoprotein (P-gp) and strong CYP3A4 Inhibitors*

Avoid coadministration of Gavreto with known strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inhibitors. If coadministration with a strong CYP3A4 inhibitor or combined P-gp and strong CYP3A4 inhibitor cannot be avoided, reduce the current dose of Gavreto as recommended in Table 3. After the strong CYP3A4 inhibitor or combined P-gp and strong CYP3A4 inhibitor has been discontinued for 3 to 5 elimination half-lives, the Gavreto dose that was taken prior to the inhibitor can be resumed.

**Table 3: Recommended Dosage Modifications for Gavreto for Coadministration with Strong CYP3A4 Inhibitors or Combined P-gp and Strong CYP3A4 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 |

*Dose Modification for Use with Strong CYP3A4 Inducers*

Avoid coadministration of pralsetinib with strong CYP3A4 inducers. If coadministration with a strong CYP3A4 inducer cannot be avoided, the dose of pralsetinib should be increased to double the current pralsetinib dose starting on Day 7 of coadministration of pralsetinib with the strong CYP3A4 inducer. After the strong CYP3A4 inducer has been discontinued for at least 14 days, the Gavreto dose that was taken prior to the use of the strong CYP3A4 inducer can be resumed.

### 2.2.1 Special Dosage Instructions

**Pediatric use**

The safety and efficacy of Gavreto in pediatric patients (<18 years) have not been established.

**Geriatric use**

No dose adjustment of Gavreto is required in patients $\geqslant$ 65 years of age (see Section 3.2.5 Pharmacokinetics in Special Populations).

**Renal Impairment**

No dose adjustment is required in patients with mild and moderate renal impairment. The safety and efficacy of Gavreto have not been studied in patients with severe renal impairment (see Section 3.2.5 Pharmacokinetics in Special Populations). Since pralsetinib elimination via the kidney is negligible, no dose adjustment is required in patients with severe renal impairment or end-stage renal disease.

**Hepatic Impairment**

No dose adjustment is required for patients with mild hepatic impairment. The safety and efficacy of Gavreto have not been studied in patients with moderate or severe hepatic impairment (see Section 3.2.5 Pharmacokinetics in Special Populations).

## 2.3 CONTRAINDICATIONS

Gavreto is contraindicated in patients with a known hypersensitivity to pralsetinib or any of the excipients.

## 2.4 WARNINGS AND PRECAUTIONS

### 2.4.1 General

**Pneumonitis/Interstitial Lung Disease**

Cases of severe, life-threatening, and fatal pneumonitis/interstitial lung disease (ILD) have been reported in clinical trials with Gavreto. Patients should be monitored for acute or worsening of pulmonary symptoms indicative of pneumonitis/ILD (e.g., dyspnea, cough, and fever). Based on the severity of confirmed pneumonitis/ILD, Gavreto should be withheld, dose reduced, or permanently discontinued (see Section 2.2 Dosage and Administration).

**Hypertension**

Hypertension has been reported in clinical trials with Gavreto. 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. In case of severe and persistent hypertension, Gavreto should be withheld, dose reduced, or permanently discontinued (see Section 2.2 Dosage and Administration).

**Hepatic Transminase Elevations**

Severe hepatic laboratory abnormalities including increased AST and increased ALT have been reported in clinical trials with Gavreto. Monitor AST and ALT prior to initiating Gavreto, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. See Section 2.2 for dose modification based on the severity of the hepatic laboratory abnormality.

**Hemorrhagic events**

Severe, including fatal, hemorrhagic events can occur with Gavreto. In patients with life-threatening or recurrent severe bleeding, Gavreto should be permanently discontinued (see Section 2.2 Dosage and Administration).

**QT Prolongation**

Prolongation of the QT interval has been observed in patients who received Gavreto in clinical trials (see section 4.8). Therefore, before starting Gavreto treatment, patients should have a QTc interval $\leqslant$470 ms 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 at the end of the first week

and of the first month of 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 prolongation.

Gavreto may require interruption, dose modification, or discontinuation (see Section 2.2 Dosage and Administration).

**Embryo-Fetal Toxicity**

Based on findings from animal studies and its mechanism of action, Gavreto has the potential to cause fetal harm when administered to pregnant women (see Section 2.5 Use in Special Populations). There are no available data on the use of Gavreto in pregnant women. 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 recommended clinical dose of 400 mg once daily (see Section 2.5 Use in Special Populations and 3.3.4 Embryo-Fetal and Development Toxicity).

Female patients of reproductive potential must use effective non-hormonal contraception during treatment with Gavreto and for 2 weeks after the final dose. Gavreto may render hormonal contraceptives ineffective.

Male patients with female partners of reproductive potential must use effective contraception during treatment with Gavreto and for at least 1 week after the final dose.

**Tumor Lysis Syndrome**

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

**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.

### 2.4.2 Drug Abuse and Dependence

Not applicable

### 2.4.3 Ability to Drive and Use Machines

No studies on the effects of Gavreto on the ability to drive or use machines have been performed. Caution should be exercised when driving or operating machines as patients may experience fatigue while taking Gavreto (see section 2.6 Undesirable Effects

## 2.5 USE IN SPECIAL POPULATIONS

### 2.5.1 Females and Males of Reproductive Potential

***Fertility***

See section 3.3.3 Impairment of fertility.

***Pregnancy testing***

Verify the pregnancy status of females of reproductive potential prior to initiating Gavreto.

***Contraception***

Female patients of reproductive potential must use effective non-hormonal contraception during treatment with Gavreto and for 2 weeks after the final dose. Gavreto may render hormonal contraceptives ineffective.

Male patients with female partners of reproductive potential must use effective contraception during treatment with Gavreto and for at least 1 week after the final dose.

### 2.5.2 Pregnancy

Female patients of reproductive potential must be advised to avoid pregnancy while receiving Gavreto (see section 2.4 Warnings and Precautions). Patients receiving Gavreto should be advised of the potential hazard to the fetus. Female patients should be advised to contact their doctor, should pregnancy occur.

***Labor and Delivery***

The safe use of Gavreto during labor and delivery has not been established.

### 2.5.3 Lactation

It is not known whether Gavreto is excreted in human breast milk. No studies have been conducted to assess the impact of Gavreto on milk production or its presence in breast milk. As the potential for harm to the nursing infant is unknown, mothers should be advised to discontinue breast-feeding during treatment with Gavreto and for 1 week following the final dose.

### 2.5.4 Pediatric Use

Safety and efficacy in pediatric patients have not been established.

In nonclinical repeat-dose toxicology studies physeal dysplasia in non-human primates and increased physeal thickness and incisor tooth degeneration in rats were observed at exposures ($AUC_{0-24}$) similar to clinical exposures at the 400 mg QD dose. Refer to Section 3.3.3 for more details.

### 2.5.5 Geriatric Use

*See Sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations.*

### 2.5.6 Renal Impairment

*See Sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations.*

### 2.5.7 Hepatic Impairment

*See Sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations.*

## 2.6 UNDESIRABLE EFFECTS

### 2.6.1 Clinical Trials

***Summary of the safety profile***

The safety of Gavreto was evaluated in 471 patients treated with 400 mg QD in an open-label, single-arm study (“ARROW”). Patients with *RET*-fusion positive NSCLC, *RET*-mutant medullary thyroid cancer, and other *RET*-altered advanced solid tumors were included in the study. Patients received a starting dose of 400 mg once daily until intolerance to therapy, disease progression, or investigator determination that the patient was no longer benefiting from treatment.

***Tabulated summary of adverse drug reactions from clinical trials***

Adverse drug reactions from clinical trials (Table 4) are listed by MedDRA 19.1 system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000).

**Table 4: Summary of adverse drug reactions occurring in patients treated with Gavreto (400 mg QD) in the ARROW study (safety population)**

| System Organ Class<br>Adverse reaction | Frequency category (All Grades) | Gavreto N = 471 | |
|---|---|---|---|
| | | All Grades (%) | Grades 3-4 (%) |
| **Blood and Lymphatic System Disorders** | | | |
| Anemia[1] | very common | 40.6 | 14.9 |
| Neutropenia[2] | very common | 39.9 | 18.3 |
| Leukopenia[3] | very common | 31.4 | 6.4 |
| Lymphopenia[4] | very common | 18.0 | 10.6 |
| Thrombocytopenia[5] | very common | 16.3 | 4.2 |
| **Gastrointestinal disorders** | | | |
| Constipation | very common | 38.9 | 0.6 |
| Diarrhea | very common | 28.9 | 3.2 |
| Dry mouth | very common | 14.9 | 0 |
| Nausea | very common | 14.2 | 0.2 |
| Abdominal pain[6] | very common | 13.6 | 1.3 |
| Vomiting | very common | 10.8 | 1.1 |
| Stomatitis[7] | common | 7.0 | 1.3 |
| **General Disorders and Administration Site Conditions** | | | |
| Fatigue[8] | very common | 34.0 | 4.5° |
| Edema[9] | very common | 24.6 | 0.2 |
| Pyrexia | very common | 22.3 | 1.1 |
| **Hepatobiliary Disorders** | | | |
| Aspartate aminotransferase increased | very common | 44.2 | 5.3 |
| Alanine aminotransferase increased | very common | 31.4 | 4.2 |
| **Infection and Infestations** | | | |
| Pneumonia[10] | very common | 14.2 | 8.3[#] |
| Urinary tract infection | very common | 11.3 | 3.0° |
| **Musculoskeletal and Connective Tissue Disorders** | | | |
| Musculoskeletal pain[11] | very common | 37.2 | 1.9 |
| Blood creatine phosphokinase increased | very common | 11.9 | 4.5 |

**Table 4: Summary of adverse drug reactions occurring in patients treated with Gavreto (400 mg QD) in the ARROW study (safety population)**

| System Organ Class<br>Adverse reaction | Frequency category (All Grades) | Gavreto N = 471 | |
|---|---|---|---|
| | | All Grades (%) | Grades 3-4 (%) |
| **Nervous system disorders** | | | |
| Taste disorder[12] | very common | 15.7 | 0 |
| Headache[13] | very common | 14.4 | 0.4 |
| **Renal and Urinary Disorders** | | | |
| Blood creatinine increased | very common | 21.2 | 0.2 |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Cough[14] | very common | 22.7 | 0.6 |
| Dyspnea | very common | 15.3 | 1.7° |
| Pneumonitis[15] | very common | 10.8 | 2.8° |
| **Skin and subcutaneous tissue disorders** | | | |
| Rash[16] | very common | 16.3 | 0 |
| **Vascular Disorders** | | | |
| Hypertension[17] | very common | 30.8 | 15.3 |
| Hemorrhage[18] | very common | 17.4 | 2.8° |

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

[2] Includes the preferred terms: Neutropenia, Neutrophil count 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: Thrombocytopenia, Platelet count decreased

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

[7] Includes the preferred terms: Stomatitis, Aphthous ulcer

[8] Includes the preferred terms: Fatigue, Asthenia

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

[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

[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: Dysgeusia, Ageusia

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

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

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

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

**Table 4: Summary of adverse drug reactions occurring in patients treated with Gavreto (400 mg QD) in the ARROW study (safety population)**

| System Organ Class<br>Adverse reaction | Frequency category (All Grades) | Gavreto N = 471 | |
|---|---|---|---|
| | | All Grades (%) | Grades 3-4 (%) |

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

[18] Includes the preferred terms identified using the MedDRA 19.1 SMQ Haemorrhage (excl laboratory terms) narrow

° Additionally, 1 (0.2%) Grade 5 event was reported

# Additionally, 6 (1.3%) Grade 5 events were reported

### *Laboratory Abnormalities*

The following table provides treatment-emergent shifts from baseline in laboratory abnormalities occurring in patients treated with Gavreto in the ARROW study.

**Table 5 Gavreto Treatment-emergent shifts of key laboratory abnormalities worsening from baseline in ≥ 20% Patients who Received Gavreto 400 mg QD in the ARROW study (safety population)**

| Laboratory Test Abnormality | Gavreto 400 mg QD N=471 | |
|---|---|---|
| | Worsen to Grade 1-4 (%) | Worsen to Grade 3-4 (%) |
| **Hematology** | | |
| Decreased Hemoglobin | 63.7 | 11.5 |
| Decreased Neutrophils | 62.4 | 18.7 |
| Decreased Lymphocytes | 60.3 | 24.2 |
| Decreased Platelets | 29.7 | 4.5 |
| **Chemistry** | | |
| Increased Aspartate Aminotransferase (AST) | 73.9 | 5.1 |
| Decreased Calcium Corrected | 50.3 | 5.1 |
| Increased Alanine Aminotransferase (ALT) | 50.3 | 4.7 |
| Decreased Albumin | 40.3 | 0.8 |
| Increased Creatinine | 36.7 | 0.8 |
| Increased Alkaline Phosphatase | 33.1 | 1.9 |
| Decreased Phosphate | 32.7 | 10.6 |
| Decreased Sodium | 28.9 | 4.7 |
| Increased Bilirubin | 21.0 | 1.5 |

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

### 2.6.2 Postmarketing Experience

Not applicable.

## 2.7 OVERDOSE

There is no experience with overdosage in human clinical trials with Gavreto. Patients who experience overdose should be closely supervised and supportive care instituted. There is no specific antidote for overdose with Gavreto.

## 2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

*In vitro* data indicate that pralsetinib is primarily metabolised by CYP3A4 and transported by P-gp. Therefore, inducers and inhibitors of CYP3A4 and P-gp may alter the plasma concentrations of pralsetinib.

**Effects of Other Drugs on Pralsetinib**

***Strong CYP3A4 Inhibitors and Combined P-gp and Strong CYP3A4 Inhibitors***

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

Coadministration of pralsetinib with a strong CYP3A4 inhibitor or combined P-gp and strong CYP3A4 inhibitor may increase pralsetinib plasma concentrations and may result in increased adverse reactions. Avoid coadministration of Gavreto with strong CYP3A4 inhibitors or with combined P-gp and strong CYP3A4 inhibitors. If coadministration with a combined P-gp and strong CYP3A4 inhibitor cannot be avoided, reduce the Gavreto dose (see Section 2.2 Dosage and Administration).

***Strong CYP3A4 Inducers***

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

Coadministration of pralsetinib with a strong CYP3A4 inducer may decrease pralsetinib plasma concentrations and may result in decreased efficacy of pralsetinib. Avoid coadministration of Gavreto with strong CYP3A4 inducers. If coadministration cannot be avoided, increase the Gavreto dose (see Section 2.2 Dosage and Administration).

### *P-gp inhibitors*

P-gp inhibitors may decrease the gastrointestinal secretion of pralsetinib and potentially increase its plasma concentration. No clinical drug interaction studies have been performed.

## 3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

## 3.1 PHARMACODYNAMIC PROPERTIES

### 3.1.1 Mechanism of Action

Pralsetinib is a tyrosine kinase inhibitor that targets oncogenic *RET* fusions and mutations, including V804 gatekeeper mutations associated with resistance to other therapies. *In vitro*, pralsetinib inhibited several oncogenic *RET* fusions and mutations (CCDC6 *RET*, *RET* V804L, *RET* V804M and *RET* M918T) with half maximal inhibitory concentrations at clinically relevant concentrations. In a broad panel of purified enzyme assays, pralsetinib demonstrated selectivity for *RET* with 81-fold selectivity over VEGFR2.

*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 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).

#### Cardiac Electrophysiology

The QT interval prolongation potential of pralsetinib was assessed in 34 patients with *RET*-positive solid tumors administered at 400 mg once daily. No clinically relevant mean increase in QTc (i.e.> 20 ms) was detected in the study. No effect on heart rate or cardiac conduction (PR, QRS, and RR intervals) was observed.

### 3.1.2 Clinical / Efficacy Studies

The efficacy of Gavreto was demonstrated in a multi-center, open-label clinical trial in adults (ARROW). Patients with *RET*-fusion positive NSCLC, thyroid cancer, and other *RET*-altered advanced solid tumors were included in the study. Identification of a *RET* gene alteration was determined by local laboratories using next generation sequencing (NGS), fluorescence in situ hybridization (FISH), and other tests.

Efficacy was established on the basis of overall response rate (ORR) according to RECIST v1.1 and duration of response (DOR), as evaluated by a Blinded Independent Central Review (BICR). Additional efficacy outcome measures included disease control rate (DCR) and Clinical Benefit Rate (CBR) also evaluated by a BICR.

## Metastatic *RET*-Fusion Positive NSCLC

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

The assessment of efficacy was based on a total of 87 patients with *RET* fusion-positive NSCLC with measurable disease at baseline and sufficient evidence of a *RET* alteration who received prior platinum-based chemotherapy treated with Gavreto at a starting doses of 400 mg once daily.

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%), all patients (100%) 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) (MDP)**

| **Efficacy Parameter** | **Previously treated with platinum chemotherapy (N=87)** | **Previously treated with systemic treatment (N=98)** | **Treatment-naïve (N=27)** |
|---|---|---|---|
| **Overall Response Rate (ORR)[a]**, % (95% CI) | 57.5 (46.4, 68.0) | 58.2 (47.8, 68.1) | 70.4 (49.8, 86.2) |
| Complete Response, % | 5.7 | 5.1 | 11.1 |
| Partial Response, % | 51.7 | 53.1 | 59.3 |
| **Duration of Response (DOR)** | **(N=50)** | **(N=57)** | **(N=19)** |
| Median, months (95% CI) | 17.1 (15.2-17.1) | 17.1 (15.2, NE) | 9.0 (6.3, NE) |
| Patients with DOR ≥ 6-months[b], % | 76.5 | 77.6 | 47.4 |

MDP = measurable disease population

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 previously treated with an anti-PD-1 or anti-PD-L1 therapy, an exploratory subgroup analysis of ORR was 59% (95% CI: 42, 74) and the median DOR was not reached (95% CI: 11.3, NR).

Among all patients previously treated with platinum, the BICR response rates by *RET* fusion partner to Gavreto were:

- ORR= 59% (95% CI: 46, 71) in 65 patients with a KIF5B fusion partner
- ORR = 60% (95% CI: 32, 84) in 15 patients with a CCDC6 fusion partner.

The RECIST CNS ORR assessed by BICR was 5 out of 9 response evaluable patients with brain metastases at baseline, including 3 patients with a CNS complete response. No patients without history of CNS involvement and receiving a starting dose of 400 mg QD developed new CNS metastases on study.

*Treatment-naïve RET Fusion-Positive NSCLC*

Efficacy was evaluated in 27 patients with treatment-naïve *RET* fusion-positive NSCLC who were not candidates for platinum-based chemotherapy 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 and 37% had either history or current CNS metastasis. The most common *RET* fusion partners were KIF5B (70%) and CCD6 (11%). *RET* fusions were detected in 67% of patients using NGS (41% tumor samples; 22% blood or plasma; 4% unknown) and 33% using FISH.

Efficacy results for treatment-naïve *RET* fusion-positive NSCLC are summarized in Table 6.

Among the patients who were treatment naïve, the BICR response rates by *RET* fusion partner to Gavreto were:

- ORR= 79% (95% CI: 54, 94) in 19 patients with a KIF5B fusion partner
- ORR= 67% (95% CI: 9, 99) in 3 patients with a CCDC6 fusion partner.

**_RET_-Mutant Medullary Thyroid Cancer**

The efficacy of Gavreto was demonstrated in patients with *RET*-mutant MTC in a multicenter, open-label, multi-cohort clinical trial (ARROW). Of the 145 RET-mutant MTC patients treated with 400mg QD in the efficacy population 49 (34%) were reported as stage IV, 11 (8%) stage IVa, 16 (11%) stage IVb and 69 (48%) stage IVc.

*RET-Mutant MTC Previously Treated with Cabozantinib and/or Vandetanib*

Efficacy was evaluated in 55 patients with *RET*-mutant advanced MTC previously treated with cabozantinib or vandetanib (or both).

The median age was 59 years (range: 25 to 83); 69% were male, 78% were White, 6% were Asian, 6% were Hispanic/Latino. ECOG performance status was 0-1 (94%) or 2 (6%), all patients (100%) had metastatic disease, and 7.3% had a history of CNS metastases. Patients had received a median of 2 prior therapies (range 1-6). *RET* mutation status was detected in 73% using NGS [55% tumor sample, 18% plasma], 26% using PCR sequencing, and 2% other. The primary mutations in *RET*-mutant MTC previously treated with cabozantinib and/or vandetanib are described in Table 7.

**Table 7: Primary Mutations in *RET*-Mutant MTC in ARROW**

| ***RET* Mutation Type** | **Prior Cabozantinib and/or Vandetanib (n= 55)** | **Treatment Naïve (n=21)** | **Total (n=84)** |
|---|---|---|---|
| M918T | 37 | 8 | 52 |
| Cysteine Rich Domain[1] | 12 | 10 | 23 |
| V804M or V804L[2] | 2 | 1 | 3 |
| Other[3] | 4 | 2 | 6 |

[1] Cysteine Rich Domain (including the following cysteine residues: 609, 611, 618, 620, 630, and/or 634)

[2] All patients also had a M918T mutation

[3] Other included: D898_E901del (1), L790F (1), A883F (2), K666E (1), and R844W (1)

Efficacy results are summarized in Table 8. The median time to first response was 3.7 months (range: 1.8-12.9 months).

**Table 8: Efficacy Results for *RET*-Mutant MTC (ARROW) (MDP)**

| | ***RET*-Mutant MTC** | |
|---|---|---|
| | **Previously Treated with Cabozantinib and/or Vandetanib** | **Treatment-naïve** |
| **Efficacy Parameters** | **Gavreto (N=55)** | **Gavreto (N=21)** |
| **Overall Response Rate (ORR)[a]**, % (95% CI) | 60.0 (45.9, 73.0) | 71.4 (47.8, 88.7) |
| Complete Response, % | 1.8 | 4.8 |
| Partial Response, % | 58.2 | 66.7 |
| **Duration of Response (DOR)** | **(N=33)** | **(N=15)** |
| Median in months (95% CI) | NE (15.1, NE) | NE (NE, NE) |
| Patients with DOR ≥ 6 months[b], % | 78.8 | 80.0 |

*Treatment-naïve RET-Mutant MTC*

Efficacy was evaluated in 21 patients with treatment-naïve *RET*-mutant advanced MTC who were not candidates for standard systemic therapies.

The median age was 64 years (range: 19 to 81); 76% were male, 76% were White, 19% were Asian, 5% were Hispanic/Latino. ECOG performance status was 0-1 (100%), all patients (100%) had metastatic disease, and 19% had a history of CNS metastases. *RET* mutation status was detected in 86% using NGS [43% tumor sample, 38% plasma, 1% blood] and 14% using PCR sequencing. The primary mutations in treatment-naïve *RET*-mutant MTC are described in Table 7.

Efficacy results for treatment-naïve *RET*-mutant MTC are summarized in Table 8. The median time to first response was 5.6 months (range: 1.8-11.1 months).

### 3.1.3 Immunogenicity

Not applicable.

## 3.2 PHARMACOKINETIC PROPERTIES

Following administration of pralsetinib once daily, steady state was reached by 3-5 days. After single dose and repeat dosing of pralsetinib once daily, a dose-dependent increase in systemic exposure was observed over the dose range of 60-600 mg; however, the increase was not dose proportional. At 400 mg QD dosing, the steady-state mean accumulation ratio (%CV) based on AUC was 2.46 (1.83%). The steady state geometric mean [% coefficient of variation (CV%)] of maximum observed plasma concentration ($C_{max}$) and area under the

concentration-time curve ($AUC_{0-24h}$) of pralsetinib at 400 mg was 2470 (55.1%) ng/mL and 36700 (66.3%) h•ng/mL, respectively.

### 3.2.1 Absorption

Following administration of single oral doses of pralsetinib of 60 to 600 mg, the median time to peak concentration ($T_{max}$) ranged from 2 to 4 hours postdose.

**Effect of food**

Food had an effect on both the rate and extent of absorption. Pralsetinib $C_{max}$ and $AUC_{0-inf}$ were increased by 104% and 122%, respectively in healthy subjects who were administered pralsetinib after a standardized high-fat meal (~800-1000 calories and ~50 – 60% of calories from fat) compared to the $C_{max}$ and $AUC_{0-inf}$ after overnight fasting.

Food delayed the absorption of pralsetinib with a statistically significant (p-value <.0001) and the median $T_{max}$ was delayed (4 hours under fasted conditions vs. 8.5 hours under fed conditions).

Gavreto is recommended to be administered on an empty stomach.

### 3.2.2 Distribution

Pralsetinib is 97.1% bound to human plasma proteins *in vitro* and the binding is not concentration-dependent. The blood-to-plasma ratio is 0.6 to 0.7. Following a single 400 mg oral dose of pralsetinib, the geometric mean (CV%) apparent volume of distribution (Vd/F) of pralsetinib was 303L (68%) indicating extensive distribution into tissues from plasma.

### 3.2.3 Metabolism

*In vitro* studies demonstrated that the oxidative metabolism of pralsetinib is primarily mediated by CYP3A4 with minor contribution from CYP2D6 and CYP1A2; while glucuronidation is primarily catalyzed by UGT1A4. 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.

### 3.2.4 Elimination

The mean (±standard deviation) plasma elimination half-life of pralsetinib was 15.7 hours (9.8) following single doses and 20 (11.7) hours following multiple doses of pralsetinib.

Following oral administration of pralsetinib 400 mg once daily, the steady state geometric mean apparent oral clearance (CL/F) was 10.9 L/h (66%).

Following a single oral dose of ~ 310 mg administered as 3 x 100 mg capsules plus one capsule containing ~10 mg (~100 µCi) [$^{14}$C]pralsetinib to healthy

subjects, 73% of the radioactive dose was recovered in feces and 6% was recovered in urine. Unchanged pralsetinib represented approximately 66% and 4.8% of the total radioactive dose in feces and urine, respectively.

### 3.2.5 Pharmacokinetics in Special Populations

No clinically significant differences in the pharmacokinetics of pralsetinib were observed based on age (19 to 87 years), sex, race (370 White, 22 Black, or 61 Asian), and body weight (32.1 to 128 kg).

**Pediatric Population**

The safety and efficacy of Gavreto in pediatric patients (<18 years) have not been established.

**Geriatric Population**

Data obtained in geriatric patients show that pharmacokinetic parameters for Gavreto are not significantly affected in this population.

**Renal impairment**

Based on a population pharmacokinetic analysis, Gavreto exposures were similar among 94 subjects with mild renal impairment ($CL_{CR}$ 60-89 mL/min), 12 subjects with moderate renal impairment ($CL_{CR}$ 30-59 mL/min) and 76 subjects with normal renal function ($CL_{CR} \geqslant 90$ mL/min). The pharmacokinetics of Gavreto in patients with severe renal impairment ($CL_{CR}$ 15-29 mL/min) or end-stage renal disease ($CL_{CR}$ <15 mL/min) have not been studied.

**Hepatic impairment**

As hepatic elimination is a major route of excretion for Gavreto, hepatic impairment may result in increased plasma concentrations. Based on a population pharmacokinetic analysis, Gavreto exposures were similar between 7 subjects with mild hepatic impairment (total bilirubin within upper limit of normal [ULN] and AST > ULN or total bilirubin >1 to 1.5 times ULN and any AST) and 175 subjects with normal hepatic function (total bilirubin and AST within ULN). The pharmacokinetics of Gavreto in patients with moderate (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 times ULN and any AST) have not been studied.

## 3.3 NONCLINICAL SAFETY

### 3.3.1 Carcinogenicity

Carcinogenicity studies with pralsetinib have not been conducted.

### 3.3.2 Genotoxicity

Pralsetinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay, with and without metabolic activation. Pralsetinib was negative in both *in vitro* human lymphocyte chromosome aberration assay and *in vivo* rat bone marrow micronucleus tests.

### 3.3.3 Impairment of Fertility

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, post-implantation loss occurred at ≥5 mg/kg (approximately 0.35 times the human exposure (AUC) at the clinical dose of 400 mg based on toxicokinetic data from the 13-week rat toxicology study). At the 20 mg/kg dose level (approximately 2.9 times the human exposure (AUC) at the clinical dose of 400 mg based on toxicokinetic data from the 13-week rat toxicology study) 82% of female rats had totally resorbed litters, with 92% post-implantation loss (early resorptions). In a 13-week repeat-dose toxicology study, male rats exhibited histopathological evidence of tubular degeneration/atrophy in the testis with secondary cellular debris and reduced sperm in the lumen of the epididymis, which correlated with lower mean testis and epididymis weights and gross observations of soft and small testis. Female rats exhibited degeneration of the corpus luteum in the ovary. For both sexes, these effects were observed at pralsetinib doses ≥10 mg/kg/day, approximately 1 times the human exposure based on AUC at the clinical dose of 400 mg.

No findings were noted in the reproductive organs in a 13-week repeated-dose toxicology study in sexually immature monkeys at dose levels up to 10 mg/kg/day (approximately 1x the human exposure at the 400 mg once daily dose).

### 3.3.4 Embryo-Fetal toxicity

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

### 3.3.5 Other

**Repeat-dose toxicity studies**

In 4- and 13-week studies in rats and cynomolgus monkeys, haematological effects were observed in both species at exposures below the human exposure (AUC) at clinical dose of 400 mg. 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 incisor tooth 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. Additional adverse findings at higher exposures included hyperphosphatemia and multi-organ mineralization in rats (approximately 2 times), and hemorrhage in the heart of preterm decedents (approximately 5.3 times) relative to the human AUC at the clinical dose of 400 mg.

**Cardiovascular effects**

Increased blood pressure was observed in rats after a single dose of 25 mg/kg (approximately 2-fold the human clinical $C_{max}$ at 400 mg based on the toxicokinetic data at 20 mg/kg from the 28-day rat toxicology study).

## 4. PHARMACEUTICAL PARTICULARS

### 4.1 STORAGE

Storage: Do not store above 30°C

Protect from moisture.

Shelf life: This medicine should not be used after the expiry date (EXP) shown on the pack.

### 4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

**Disposal of unused/expired medicines**

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

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

## 4.3 PACKS

Gavreto hard capsules are packaged in round, wide-mouth, white, HDPE bottle with dessicant and child resistant closure.

100mg hard capsules are supplied in bottles of 60 capsules and 120 capsules.

**Medicine: keep out of reach of children**

Current at April 2023

F. Hoffmann-La Roche Ltd Basel, Switzerland