Gavreto®

Pralsetinib

Hard capsules

NAME OF THE MEDICINAL PRODUCT

GAVRETO

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 100 mg of pralsetinib.

For the full list of excipients, see section 11.

PHARMACEUTICAL FORM

Hard capsules.

1 INDICATIONS AND USAGE

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

GAVRETO is indicated for the treatment of adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC).

1.2 *RET*-Mutant Medullary Thyroid Cancer

GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy.

1.3 *RET* Fusion-Positive Thyroid Cancer

GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

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

2.2 Recommended Dosage

The recommended dosage of GAVRETO is 400 mg orally once daily on an empty stomach (the capsules should be swallowed whole with a glass of water, no food intake for at least 2 hours before and at least 1 hour after taking GAVRETO*) [see Clinical Pharmacology (12.3)]*. Continue treatment until disease progression or until unacceptable toxicity.

If a dose of GAVRETO is missed, it can be taken as soon as possible on the same day. Resume the regular daily dose schedule for GAVRETO the next day.

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

2.3 Dosage Modifications for Adverse Reactions

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

Table 1: Recommended Dose Reductions for GAVRETO for Adverse Reactions

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

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

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

Table 2: Recommended Dosage Modifications for GAVRETO for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
ILD/Pneumonitis *[see Warnings and Precautions (5.1)]*	Grade 1 or 2	Withhold GAVRETO until resolution. Resume by reducing the dose as shown in Table 1. Permanently discontinue GAVRETO for recurrent ILD/pneumonitis.
	Grade 3 or 4	Permanently discontinue for confirmed ILD/pneumonitis.
Hypertension *[see Warnings and Precautions (5.2)]*	Grade 3	Withhold GAVRETO for Grade 3 hypertension that persists despite optimal antihypertensive therapy. Resume at a reduced dose when hypertension is controlled.
	Grade 4	Discontinue GAVRETO.
Hepatotoxicity *[see Warnings and Precautions (5.3)]*	Grade 3 or 4	Withhold GAVRETO and monitor AST/ALT once weekly until resolution to Grade 1 or baseline. Resume at reduced dose (Table 1). If hepatotoxicity recurs at Grade 3 or higher, discontinue GAVRETO.
Hemorrhagic Events *[see Warnings and Precautions (5.4)]*	Grade 3 or 4	Withhold GAVRETO until recovery to baseline or Grade 0 or 1. Discontinue GAVRETO for severe or life-threatening hemorrhagic events.
Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Grade 3 or 4	Withhold GAVRETO until improvement to ≤ Grade 2. Resume at reduced dose (Table 1). Permanently discontinue for recurrent Grade 4 adverse reactions.

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

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

Avoid coadministration of GAVRETO with known combined P-gp and strong CYP3A inhibitors. If coadministration with a combined P-gp and strong CYP3A inhibitor cannot be avoided, reduce the current dose of GAVRETO as recommended in Table 3. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume GAVRETO at the dose taken prior to initiating the combined P-gp and strong CYP3A inhibitor *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

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

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

2.5 Dose Modification for Use with Strong CYP3A Inducers

Avoid coadministration of GAVRETO with strong CYP3A inducers. If coadministration with a strong CYP3A inducer cannot be avoided, increase the starting dose of GAVRETO to double the current GAVRETO dosage starting on Day 7 of coadministration of GAVRETO with the strong CYP3A inducer. After the inducer has been discontinued for at least 14 days, resume GAVRETO at the dose taken prior to initiating the strong CYP3A inducer *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 100 mg, size 0, light blue, opaque, capsule shell with white imprint “BLU-667” on the body and white imprint “100 mg” on the cap, containing white to off white powder.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 11.

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with GAVRETO. Pneumonitis occurred in 10% of patients who received GAVRETO, including 2.7% with Grade 3-4, and 0.5% with fatal reactions.

Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold GAVRETO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory

symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD *[see Dosage and Administration (2.3)]*.

5.2 Hypertension

Hypertension occurred in 29% of patients, including Grade 3 hypertension in 14% of patients *[see Adverse Reactions (6.1)]*. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications.

Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue GAVRETO based on the severity *[see Dosage and Administration (2.3)]*.

5.3 Hepatotoxicity

Serious hepatic adverse reactions occurred in 2.1% of patients treated with GAVRETO. Increased AST occurred in 69% of patients, including Grade 3 or 4 in 5% and increased ALT occurred in 46% of patients, including Grade 3 or 4 in 6% *[see Adverse Reactions (6.1)]*. The median time to first onset for increased AST was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 1.7 years).

Monitor AST and ALT prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity *[see Dosage and Administration (2.3)]*.

5.4 Hemorrhagic Events

Serious, including fatal, hemorrhagic events can occur with GAVRETO. Grade ≥ 3 hemorrhagic events occurred in 2.5% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event.

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

5.5 Tumor Lysis Syndrome

Cases of tumor lysis syndrome (TLS) have been reported in patients with medullary thyroid carcinoma receiving GAVRETO *[see Adverse Reactions (6.1)]*. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

5.6 Risk of Impaired Wound Healing

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, GAVRETO has the potential to adversely affect wound healing.

Withhold GAVRETO for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of GAVRETO after resolution of wound healing complications has not been established.

5.7 Embryo-Fetal Toxicity

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

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

Effects on ability to drive and use machines:

Gavreto has minor influence on the ability to drive and use machines. Caution should be exercised when driving or operating machines as patients may experience fatigue while taking Gavreto.

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

The pooled safety population in the WARNINGS AND PRECAUTIONS reflect exposure to GAVRETO as a single agent at 400 mg orally once daily in 438 patients with *RET*-altered solid tumors, including with *RET* fusion-positive NSCLC (n = 220), and *RET*-altered thyroid cancer (n=138), in ARROW *[see Clinical Studies (14)]*. Among 438 patients who received GAVRETO, 47% were exposed for 6 months or longer and 23% were exposed for greater than one year.

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

RET Fusion-Positive Non-Small Cell Lung Cancer

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 220 patients with metastatic rearranged during transfection (*RET* fusion-positive) non-small cell lung cancer (NSCLC) in ARROW *[see Clinical Studies (14.1)]*. Among the 220 patients who received GAVRETO, 42% were exposed for 6 months or longer and 19% were exposed for greater than one year.

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

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

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

Dosage interruptions due to an adverse reaction occurred in 60% of patients who received GAVRETO. Adverse reactions requiring dosage interruption in ≥ 2% of patients included neutropenia, pneumonitis, anemia, hypertension, pneumonia, pyrexia, increased aspartate aminotransferase (AST), increased blood creatine phosphokinase, fatigue, leukopenia, thrombocytopenia, vomiting, increased alanine aminotransferase (ALT), sepsis, and dyspnea.

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

Table 4 summarizes the adverse reactions in *RET* Fusion-Positive NSCLC Patients in ARROW.

Table 4: Adverse Reactions (≥ 15%) in *RET* Fusion-Positive NSCLC Patients Who Received GAVRETO in ARROW

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

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

Table 5 summarizes the laboratory abnormalities in ARROW.

Table 5: Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in *RET* Fusion-Positive NSCLC Patients Who Received GAVRETO in ARROW

Laboratory Abnormality	GAVRETO N=220	
	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry		
Increased AST	74	2.3
Increased ALT	49	2.3
Increased alkaline phosphatase	42	1.8
Decreased calcium (corrected)	39	1.8
Decreased albumin	36	0
Decreased phosphate	35	11
Increased creatinine	33	0.5
Decreased sodium	29	7
Increased potassium	26	0.9
Hematology		
Decreased neutrophils	61	16
Decreased hemoglobin	58	9
Decreased lymphocytes	56	19
Decreased platelets	27	3.2

Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 216 to 218 patients.

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

RET-altered Thyroid Cancer

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 138 patients with *RET*-altered Thyroid Cancer in ARROW *[see Clinical Studies (14.2, 14.3)]*. Among the 138 patients who received GAVRETO, 68% were exposed for 6 months or longer, and 40% were exposed for greater than one year.

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

Serious adverse reactions occurred in 39% of patients who received GAVRETO. The most frequent serious adverse reactions (in ≥ 2% of patients) were pneumonia, pneumonitis, urinary

tract infection, pyrexia, fatigue, diarrhea, dizziness, anemia, hyponatremia, and ascites. Fatal adverse reaction occurred in 2.2% of patients; fatal adverse reactions that occurred in > 1 patient included pneumonia (n=2).

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

Dosage interruptions due to an adverse reaction occurred in 67% of patients who received GAVRETO. Adverse reactions requiring dosage interruption in ≥ 2% of patients included neutropenia, hypertension, diarrhea, fatigue, pneumonitis, anemia, increased blood creatine phosphokinase, pneumonia, urinary tract infection, musculoskeletal pain, vomiting, pyrexia, increased AST, dyspnea, hypocalcemia, cough, thrombocytopenia, abdominal pain, increased blood creatinine, dizziness, headache, decreased lymphocyte count, stomatitis, and syncope.

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

Table 6 summarizes the adverse reactions occurring in *RET*-altered Thyroid Cancer Patients in ARROW.

Table 6: Adverse Reactions (≥ 15%) in *RET*-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW

Adverse Reactions	GAVRETO N=138	
	Grades 1-4 (%)	Grades 3-4 (%)
Musculoskeletal		
Musculoskeletal Pain[1]	42	0.7*
Gastrointestinal		
Constipation	41	0.7*
Diarrhea[2]	34	5*
Abdominal Pain[3]	17	0.7*
Dry mouth	17	0
Stomatitis[4]	17	0.7*
Nausea	17	0.7*
Vascular		
Hypertension	40	21*
General		
Fatigue[5]	38	6*
Edema[6]	29	0
Pyrexia	22	2.2*
Nervous System		
Headache[7]	24	0
Peripheral Neuropathy[8]	20	0
Dizziness[9]	19	0.7*
Dysgeusia[10]	17	0
Respiratory		
Cough[11]	27	1.4*
Dyspnea[12]	22	2.2*
Skin and Subcutaneous		
Rash[13]	24	0
Metabolism and Nutrition		
Decreased Appetite	15	0

[1] Musculoskeletal Pain includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain
[2] Diarrhea includes colitis, diarrhea

[3] Abdominal Pain includes abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness, epigastric discomfort
[4] Stomatitis includes mucosal inflammation, stomatitis, tongue ulceration
[5] Fatigue includes asthenia, fatigue
[6] Edema includes eyelid edema, face edema, edema, edema peripheral, periorbital edema
[7] Headache includes headache, migraine
[8] Peripheral neuropathy includes dysaesthesia, hyperaesthesia, hypoaesthesia, neuralgia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, polyneuropathy
[9] Dizziness includes dizziness, dizziness postural, vertigo
[10] Dysgeusia includes ageusia, dysgeusia
[11] Cough includes cough, productive cough, upper-airway cough syndrome
[12] Dyspnea includes dyspnea, dyspnea exertional
[13] Rash includes dermatitis, dermatitis acneiform, eczema, palmar-plantar, erythrodysaesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular
* Only includes a Grade 3 adverse reaction

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

Table 7 summarizes the laboratory abnormalities occurring in *RET*-altered Thyroid Cancer Patients in ARROW.

Table 7: Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in *RET*-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW

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

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important.

It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the

National Regulation by using an online form: sideeffects.health.gov.il/

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on GAVRETO

Strong CYP3A Inhibitors

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

Avoid coadministration of GAVRETO with combined P-gp and strong CYP3A inhibitors. If coadministration with a combined P-gp and strong CYP3A inhibitor cannot be avoided, reduce the GAVRETO dose *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

Strong CYP3A Inducers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Data

Animal Data

In an embryo-fetal development study, once daily oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in 100% post-implantation loss at dose levels ≥20 mg/kg (approximately 1.8 times the human exposure based on area under the curve [AUC] at the clinical dose of 400 mg). Post-implantation loss also occurred at the 10 mg/kg dose level (approximately 0.6 times the human exposure based on AUC at the clinical dose of 400 mg). Once daily oral administration of pralsetinib at dose levels ≥ 5 mg/kg (approximately 0.2 times the human AUC at the clinical dose of 400 mg) resulted in an increase in visceral malformations

and variations (absent or small kidney and ureter, absent uterine horn, malpositioned kidney or testis, retroesophageal aortic arch) and skeletal malformations and variations (vertebral and rib anomalies and reduced ossification).

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Females

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

Males

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

Infertility

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

8.4 Pediatric Use

The safety and effectiveness of GAVRETO have been established in pediatric patients aged 12 years and older for *RET*-mutant MTC and *RET*-fusion thyroid cancer. Use of GAVRETO in this age group is supported by evidence from an adequate and well-controlled study of GAVRETO in

adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the pharmacokinetics of pralsetinib, that the exposure of pralsetinib is expected to be similar between adults and pediatric patients aged 12 years and older, and that the course of *RET*-mutant MTC and *RET*-fusion thyroid cancer is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients*[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)]*.

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

Animal Toxicity Data

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

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

8.5 Geriatric Use

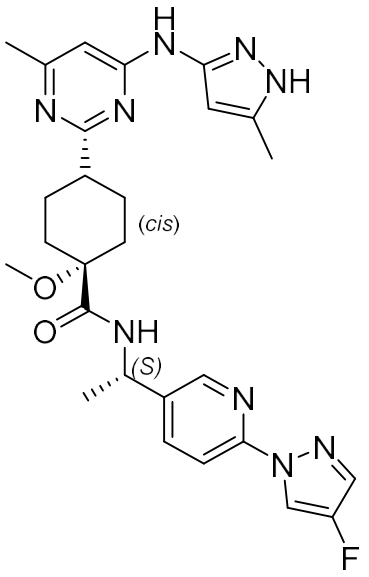
Of the 438 patients in ARROW who received the recommended dose of GAVRETO at 400 mg once daily, 30% were 65 years or older. No overall differences in pharmacokinetics (PK), safety or efficacy were observed in comparison with younger patients.

8.6 Hepatic Impairment

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

11 DESCRIPTION

Pralsetinib is an oral receptor tyrosine kinase inhibitor. The chemical name for pralsetinib is (*cis*)-*N*-((*S*)-1-(6-(4-fluoro-1*H*-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidin-2-yl)cyclohexanecarboxamide. The molecular formula for pralsetinib is $C_{27}H_{32}FN_9O_2$, and the molecular weight is 533.61 g/mol. Pralsetinib has the following structure:



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

GAVRETO (pralsetinib) is supplied for oral use as immediate release hydroxypropyl methylcellulose (HPMC) hard capsules containing 100 mg pralsetinib.

The capsules also contain inactive ingredients:

Hydroxypropyl methylcellulos, sodium bicarbonate, microcrystalline cellulose (Avicel PH102), citric acid anhydrous, pregelatinized starch, magnesium stearate, methanol.

Capsule shell:

Hypromellose, titanium dioxide FD&C Blue #1 (Brilliant Blue FCF), print ink.

The white printing ink contains Shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, purified water potassium hydroxide, and titanium dioxide is used.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2 Pharmacodynamics

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

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

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

Absorption

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

Food Effect

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

Distribution

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

Elimination

The mean (±standard deviation) plasma elimination half-life ($T_{½}$) of pralsetinib is 15.7 hours (9.8) following single doses and 20 hours (11.7) following multiple doses of pralsetinib. The mean (CV%) apparent oral clearance (CL/F) of pralsetinib is 10.9 L/h (66%) at steady state.

Metabolism

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

Excretion

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

Specific Populations

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

Patients with Hepatic Impairment

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

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

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

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

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

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

In Vitro Studies

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

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

Transporter Systems: Pralsetinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but not a substrate of bile salt efflux pump (BSEP), organic cation

transporter [OCT]1, OCT2, organic anion transporting polypeptide [OATP]1B1, OATP1B3, multidrug and toxin extrusion [MATE]1, MATE2-K, organic anion transporter [OAT]1, or OAT3.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

In a dedicated fertility and early embryonic development study conducted in treated male rats mated to treated female rats, although pralsetinib did not have clear effects on male or female mating performance or ability to become pregnant, at the 20 mg/kg dose level (approximately 2.9 times the human exposure (AUC) at the clinical dose of 400 mg based on toxicokinetic data from the 13-week rat toxicology study) 82% of female rats had totally resorbed litters, with 92% post-implantation loss (early resorptions); post-implantation loss occurred at doses as low as 5 mg/kg (approximately 0.35 times the human exposure (AUC) at the clinical dose of 400 mg based on toxicokinetic data from the 13-week rat toxicology study). In a separate fertility and early embryonic development study in which male rats administered 20 mg/kg pralsetinib were mated to untreated female rats, there were no clear pralsetinib-related effects on intrauterine survival of embryos or on male reproductive performance at a dose approximately 1.7 times the human exposure (AUC) at the clinical dose of 400 mg. In a 13-week repeat-dose toxicology study, male rats exhibited histopathological evidence of tubular degeneration/atrophy in the testis with secondary cellular debris and reduced sperm in the lumen of the epididymis, which correlated with lower mean testis and epididymis weights and gross observations of soft and small testis. Female rats exhibited degeneration of the corpus luteum in the ovary. For both sexes, these effects were observed at pralsetinib doses ≥ 10 mg/kg/day, approximately 1 times the human exposure based on AUC at the clinical dose of 400 mg.

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

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

The efficacy of GAVRETO was evaluated in patients with *RET* fusion-positive metastatic NSCLC in a multicenter, non-randomized, open-label, multi-cohort clinical trial (ARROW, NCT03037385). The study enrolled, in separate cohorts, patients with metastatic *RET* fusion-positive NSCLC who had progressed on platinum-based chemotherapy and treatment-naïve patients with metastatic NSCLC. Identification of a *RET* gene fusion was determined by local laboratories using next generation sequencing (NGS), fluorescence in situ hybridization (FISH), and other tests. Among the 114 patients in the efficacy population(s) described in this section, samples from 59% of patients were retrospectively tested with the Life Technologies Corporation Oncomine Dx Target Test (ODxTT). Patients with asymptomatic central nervous system (CNS) metastases, including patients with stable or decreasing steroid use within 2 weeks prior to study entry, were enrolled. Patients received GAVRETO 400 mg orally once daily until disease progression or unacceptable toxicity.

The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as assessed by a blinded independent central review (BICR) according to RECIST v1.1.

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

Efficacy was evaluated in 87 patients with *RET* fusion-positive NSCLC with measurable disease who were previously treated with platinum chemotherapy enrolled into a cohort of ARROW.

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

Efficacy results for *RET* fusion-positive NSCLC patients who received prior platinum-based chemotherapy are summarized in Table 8.

Table 8: Efficacy Results in ARROW (Metastatic *RET* Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy)

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

NE = not estimable
[a] Confirmed overall response rate assessed by BICR
[b] Based on observed duration of response

For the 39 patients who received an anti-PD-1 or anti-PD-L1 therapy, either sequentially or concurrently with platinum-based chemotherapy, an exploratory subgroup analysis of ORR was 59% (95% CI: 42, 74) and the median DOR was not reached (95% CI: 11.3, NE).

Among the 87 patients with *RET*-fusion positive NSCLC, 8 had measurable CNS metastases at baseline as assessed by BICR. No patients received radiation therapy (RT) to the brain within 2 months prior to study entry. Responses in intracranial lesions were observed in 4 of these 8 patients including 2 patients with a CNS complete response; 75% of responders had a DOR of ≥ 6 months.

Treatment-naïve *RET* Fusion-Positive NSCLC

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

The median age was 65 years (range 30 to 87); 52% were female, 59% were White, 33% were Asian, and 4% were Hispanic or Latino. ECOG performance status was 0-1 for 96% of the patients and all patients (100%) had metastatic disease; 37% had either history of or current CNS metastasis. *RET* fusions were detected in 67% of patients using NGS (41% tumor samples; 22% blood or plasma; 4% unknown) and 33% using FISH. The most common *RET* fusion partners were *KIF5B* (70%) and *CCDC6* (11%).

Efficacy results for treatment-naïve *RET* fusion-positive NSCLC are summarized in Table 9.

Table 9: Efficacy Results for ARROW (Treatment-Naïve Metastatic *RET* Fusion-Positive NSCLC

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

NE = not estimable
[a] Confirmed overall response rate assessed by BICR
[b] Based on observed duration of response

14.2 *RET*-Mutant Medullary Thyroid Cancer

The efficacy of GAVRETO was evaluated in patients with *RET*-mutant MTC in a multicenter, open-label, multi-cohort clinical trial (ARROW; NCT03037385).

RET-Mutant MTC Previously Treated with Cabozantinib or Vandetanib

Efficacy was evaluated in 55 patients with *RET*-mutant metastatic 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, 5% were Asian, 5% were Hispanic/Latino. ECOG performance status was 0-1 (95%) or 2 (5%), and 7% had a history of CNS metastases. Patients had received a median of 2 prior therapies (range 1-7). *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 or vandetanib are described in Table 10.

Table 10: Primary Mutations in *RET*-Mutant MTC in ARROW

***RET* Mutation Type**	**Prior Cabozantinib or Vandetanib (n= 55)**	**Cabozantinib and Vandetanib-Naïve (n=29)**	**Total (n=84)**
M918T[1]	37	15	52

Cysteine Rich Domain[2]	11	11	22
V804M or V804L	2	1	3
Other[3]	5	2	7

1 Three patients (all in the prior cabozantinib and/or vandetanib group) also had a V804M/L mutation.
2 Cysteine Rich Domain (including the following cysteine residues: 609, 611, 618, 620, 630, and/or 634)
3 Other included: D898_E901del (1), E632_L633del (1), L790F (1), A883F (2), K666E (1), and R844W (1)

Efficacy results for *RET*-mutant MTC are summarized in Table 11.

Table 11: Efficacy Results for *RET*-Mutant MTC Previously Treated with Cabozantinib or Vandetanib (ARROW)

Efficacy Parameters	**GAVRETO (N=55)**
Overall Response Rate (ORR)[a] (95% CI)	60 (46, 73)
Complete Response, %	1.8
Partial Response, %	58
Duration of Response (DOR)	**(N=33)**
Median in months (95% CI)	NR (15.1, NE)
Patients with DOR ≥ 6 months[b], %	79

NR = Not Reached; NE = Not Estimable
[a] Confirmed overall response rate assessed by BICR
[b] Based on observed duration of response

Cabozantinib and Vandetanib-naïve *RET*-mutant MTC

Efficacy was evaluated in 29 patients with *RET*-mutant advanced MTC who were cabozantinib and vandetanib treatment-naïve.

The median age was 61 years (range: 19 to 81); 72% were male, 76% were White, 17% were Asian, 3.4% were Hispanic/Latino. ECOG performance status was 0-1 (100%), 97% had metastatic disease, and 14% had a history of CNS metastases. Twenty-eight percent (28%) had received up to 3 lines of prior systemic therapy (including 10% PD-1/PD-L1 inhibitors, 10% radioactive iodine, 3.4% kinase inhibitors). *RET* mutation status was detected in 90% using NGS [52% tumor sample, 35% plasma, 3.4% blood] and 10% using PCR sequencing. The primary mutations used to identify and enroll patients are described in Table 10.

Efficacy results for cabozantinib and vandetanib-naïve *RET*-mutant MTC are summarized in Table 12.

Table 12: Efficacy Results for Cabozantinib and Vandetanib-naïve *RET*-Mutant MTC (ARROW)

Efficacy Parameters	**GAVRETO (N=29)**
Overall Response Rate (ORR)[a] (95% CI)	66 (46, 82)
Complete Response, %	10
Partial Response, %	55
Duration of Response (DOR)	**(N=19)**
Median in months (95% CI)	NR (NE, NE)
Patients with DOR ≥ 6 months[b], %	84

NR = Not Reached; NE = Not Estimable
[a] Confirmed overall response rate assessed by BICR
[b] Based on observed duration of response

14.3 *RET* Fusion-Positive Thyroid Cancer

The efficacy of GAVRETO was evaluated in *RET* fusion-positive metastatic thyroid cancer patients in a multicenter, open-label, multi-cohort clinical trial (ARROW, NCT03037385). All patients with *RET* fusion-positive thyroid cancer were required to have disease progression following standard therapy, measurable disease by RECIST version 1.1, and have *RET* fusion status as detected by local testing (89% NGS tumor samples and 11% using FISH).

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

Efficacy results are summarized in Table 13.

Table 13: Efficacy Results for *RET* Fusion-Positive Thyroid Cancer (ARROW)

Efficacy Parameters	**GAVRETO N=9**
Overall Response Rate (ORR)[a] (95% CI)	89 (52, 100)
Complete Response, %	0
Partial Response, %	89
Duration of Response (DOR)	**(N=8)**

Median in months (95% CI)	NR (NE, NE)
Patients with DOR ≥ 6 months[b], %	100

NR = Not Reached; NE = Not Estimable
[a] Confirmed overall response rate assessed by BICR
[b] Based on observed duration of response

16 HOW SUPPLIED/STORAGE AND HANDLING

GAVRETO (pralsetinib) 100 mg, size 0, light blue, opaque, capsule shell with white imprint "BLU-667" on the body and white imprint "100 mg" on the cap, containing white off white powder, are supplied as follows:

- Bottles of 60 capsules
- Bottles of 90 capsules
- Bottles of 120 capsules

Not all the pack sizes might be marketed.

Do not store above 30°C, keep the bottle tightly closed in order to protect from moisture.

Shelf life

The expiry date of the product is indicated on the packaging materials.

MARKETING AUTHORISATION HOLDER

Roche Pharmaceuticals (Israel) Ltd. P.O.B. 6391, Hod Hasharon, 4524079.

MARKETING AUTORISATION NUMBER(S)

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MANUFACTURER

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