1. NAME OF THE MEDICINAL PRODUCT

GAVRETO 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 100 mg of pralsetinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Light blue, opaque hard capsule, size 0 with "BLU-667" printed on the capsule shell body and "100 mg" on the capsule shell cap in white ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-Small Cell Lung Cancer (NSCLC)

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

RET-Mutant Medullary Thyroid Cancer (MTC)

Gavreto is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant MTC who require systemic therapy.

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).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the administration of anticancer medicinal products.

Patient selection for treatment of RET-gene fusion (NSCLC or thyroid cancer) or a RET-gene mutation (MTC) should be based on a validated test method.

Posology

The recommended dose is 400 mg pralsetinib once daily on an empty stomach (see method of administration). Treatment should be continued until disease progression or unacceptable toxicity.

If vomiting occurs after taking a dose of pralsetinib, the patient should not take an additional dose but continue with the next scheduled dose.

Missed doses
If a dose of pralsetinib is missed, the patient should make up for the missed dose as soon as possible on the same day. The regular daily dose schedule for pralsetinib should be resumed the next day.

Dose modifications for adverse reactions
Interruption of treatment with or without dose reduction may be considered to manage adverse reactions based on severity and clinical presentation.

Patients may have their dose reduced by 100 mg decrements to a minimum dose of 100 mg once daily. Gavreto should be permanently discontinued in patients who are unable to tolerate 100 mg orally once daily.

Recommended dose modifications for adverse reactions are indicated in Table 1.

Table 1. Recommended dose modifications for Gavreto for adverse reactions

Adverse reaction	**Severity[a]**	**Dose modification**
Pneumonitis/Interstitial lung disease (ILD) (see section 4.4)	Grade 1 or 2	Interrupt treatment with Gavreto until resolution. Resume at a reduced dose. Permanently discontinue Gavreto for recurrent pneumonitis/ILD.
	Grade 3 or 4	Permanently discontinue for pneumonitis/ILD.
Hypertension	Grade 3	Interrupt treatment with Gavreto for Grade 3 hypertension that persists despite optimal antihypertensive therapy. Resume at a reduced dose when hypertension is controlled.
	Grade 4	Permanently discontinue Gavreto.
Transaminase elevations	Grade 3 or 4	Interrupt treatment with Gavreto and monitor aspartate aminotransferase (AST) and alanine aminotransferase (ALT) once weekly until resolution to Grade 1 or baseline. Resume at a reduced dose. If the transaminase elevation recurs at Grade 3 or higher, permanently discontinue treatment with Gavreto.
Haemorrhagic events	Grade 3 or 4	Interrupt treatment with Gavreto until resolution to Grade 1. Resume at a reduced dose. Permanently discontinue Gavreto for life-threatening or recurrent severe haemorrhagic events.
QT prolongation	Grade 3	Interrupt treatment with Gavreto for QTc intervals >500 ms until QTc interval returns to <470 ms. Resume at the same dose if risk factors that cause QT prolongation are identified and corrected. Resume treatment at a reduced dose if other risk factors that cause QT prolongation are not identified.
	Grade 4	Permanently discontinue Gavreto if the patient has life-threatening arrhythmia.

Adverse reaction	Severity[a]	Dose modification
Other clinically significant adverse reactions (see section 4.8)	Grade 3 or 4	Interrupt treatment with Gavreto until improvement to ≤Grade 2. Resume at a reduced dose. Permanently discontinue for recurrent Grade 4 adverse reactions.

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

Dose modification for use with strong cytochrome P-450 (CYP)3A4 inhibitors or combined P-glycoprotein (P-gp) and strong CYP3A4 inhibitors
Concomitant use of pralsetinib with known strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inhibitors should be avoided (see section 4.4 and section 4.5). If co-administration with a strong CYP3A4 inhibitor or combined P-gp and strong CYP3A4 inhibitor cannot be avoided, the current dose of pralsetinib should be reduced as recommended in Table 2. After the strong CYP3A4 inhibitor or combined P-gp and strong CYP3A4 inhibitor have been discontinued for 3 to 5 elimination half-lives, the pralsetinib dose that was taken prior to the use of the inhibitor should be resumed.

Table 2. Recommended dose modifications for Gavreto for co-administration with strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inhibitors

Current Gavreto dose	Recommended Gavreto dose
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
Concomitant use of pralsetinib with strong CYP3A4 inducers should be avoided (see section 4.4 and section 4.5). If concomitant use 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 co-administration of pralsetinib with the strong CYP3A4 inducer. After the strong CYP3A4 inducer has been discontinued for at least 14 days, the pralsetinib dose that was taken prior to the use of the inducer should be resumed.

Special populations

Renal impairment
No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance [CL_{CR}] 30 to 89 mL/min estimated by Cockcroft-Gault). Pralsetinib has not been studied in patients with severe renal impairment (CL_{CR} 15 to 29 mL/min) or end-stage renal disease (CL_{CR} <15 mL/min). Since pralsetinib elimination via the kidney is negligible, no dose adjustment is required in patients with severe renal impairment or end-stage renal disease (see section 5.2).

Hepatic impairment
No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and AST > ULN or total bilirubin > 1 to 1.5 times ULN and any AST). Pralsetinib has not been studied in patients with moderate or severe hepatic impairment, therefore its use in patients with moderate or severe hepatic impairment is not recommended (see section 5.2).

Elderly
No dose adjustment is recommended for patients aged 65 years and above (see section 5.1).

Paediatric population

NSCLC
The safety and efficacy of pralsetinib in paediatric patients below 18 years of age with RET fusion-positive advanced NSCLC have not been established. No data are available.

RET-Mutant Medullary Thyroid Cancer (MTC) and RET-Fusion Positive Thyroid Cancer
No dose adjustment of Gavreto is required in pediatric patients 12 years of age and older. The safety and efficacy of Gavreto in pediatric patients under 12 years of age have not been established.

Method of administration

Gavreto is for oral use. Patients should swallow the hard capsules whole with a glass of water, on an empty stomach. They should not eat for at least two hours before and at least one hour after taking pralsetinib (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Pneumonitis/ILD

Severe, life-threatening or fatal cases of pneumonitis/ILD have been reported in patients who received pralsetinib in clinical trials (see section 4.8). Patients who present with clinically symptomatic pneumonitis or ILD were excluded from clinical trials.

Patients should be advised to contact their healthcare provider immediately to report new or worsening respiratory symptoms.

Patients who present with acute or worsening of respiratory symptoms indicative of pneumonitis/ILD (e.g., dyspnoea, cough, and fever) should be investigated to exclude other potential causes. If pneumonitis/ILD is considered to be related to pralsetinib, the dose of Gavreto should be interrupted, reduced or permanently discontinued based on severity of confirmed pneumonitis/ILD (see section 4.2).

Hypertension

Hypertension was observed in pralsetinib-treated patients in clinical trials (see section 4.8). Treatment-related hypertension was most commonly managed with anti-hypertensive medicinal products.

Treatment with Gavreto should not be initiated in patients with uncontrolled hypertension. Pre-existing hypertension should be adequately controlled before starting Gavreto treatment. Monitoring of blood pressure is recommended after 1 week, at least monthly thereafter and as clinically indicated. Anti-hypertensive therapy should be initiated or adjusted as appropriate. The dose should be interrupted, reduced, or permanently discontinued based on the severity of hypertension observed during treatment with Gavreto (see section 4.2).

Transaminase elevations

Severe cases of transaminase elevations have been reported in patients who received pralsetinib in clinical trials (see section 4.8).

ALT and AST should be monitored prior to initiating Gavreto, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Treatment with Gavreto should be

interrupted, reduced or permanently discontinued based on severity of the transaminase elevation observed during treatment with Gavreto (see section 4.2).

Haemorrhagic events

Severe, including fatal, haemorrhagic events can occur with Gavreto. In patients with life-threatening or recurrent severe haemorrhage, Gavreto should be permanently discontinued (see section 4.2).

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 ≤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 4.2).

Drug interactions

Co-administration of Gavreto with strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inhibitors should be avoided because they may increase the plasma concentration of pralsetinib (see sections 4.2 and 4.5).

Co-administration of Gavreto with strong CYP3A4 inducers should be avoided because they may decrease the plasma concentration of pralsetinib (see section 4.2 and section 4.5).

Fertility and pregnancy

During treatment with Gavreto and for at least 1 week after the final dose, male patients with female partners of childbearing potential must use effective contraception (see section 4.6).

Women of childbearing potential should be advised to avoid becoming pregnant while receiving Gavreto. A highly effective non-hormonal method of contraception is required for female patients during treatment with pralsetinib, because pralsetinib can render hormonal contraceptives ineffective. If a hormonal method of contraception is unavoidable, then a condom must be used in combination with the hormonal method. Effective contraception must be continued for at least 2 weeks after the final dose (see section 4.6).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

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.

Active substances that may have an effect on pralsetinib

Strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inhibitors
Co-administration of pralsetinib with strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inhibitors can increase pralsetinib plasma concentrations, which may increase the incidence and severity of adverse reactions of pralsetinib. Co-administration of 200 mg pralsetinib once daily with itraconazole 200 mg once daily (a strong CYP3A4 and P-gp inhibitor) increased pralsetinib C_{max} by 84% and $AUC_{0-\infty}$ by 251%, compared to pralsetinib administered alone.

Therefore, co-administration of pralsetinib with strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inhibitors (including, but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole nefazodone, grapefruit or Seville oranges) should be avoided (see section 4.4). If co-administration with strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inhibitors cannot be avoided, reduce the current dose of pralsetinib (section 4.2).

Strong CYP3A4 inducers
Co-administration of pralsetinib with strong CYP3A4 inducers can decrease pralsetinib plasma concentrations, which may decrease the efficacy of pralsetinib. Co-administration of 400 mg pralsetinib as a single dose with rifampin 600 mg once daily (a strong CYP3A4 inducer) decreased pralsetinib C_{max} by 30% and $AUC_{0-\infty}$ by 68%. Based on a population PK analysis, CYP3A4 weak inducers decreased pralsetinib exposures, but were not clinically significant in patients with NSCLC. Therefore, co-administration of pralsetinib with strong CYP3A4 inducers (including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort [*Hypericum perforatum*]) should be avoided (see section 4.4). If co-administration cannot be avoided, increase the pralsetinib dose (see section 4.2).

Sensitive substrates of CYP3A4, CYP2C8, CYP2C9, P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1 and MATE2-K with narrow therapeutic index
Co-administration of pralsetinib can alter the exposure of sensitive substrates of CYP enzymes (CYP3A4, CYP2C9 and CYP2C8) and transporters (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1 and MATE2-K). Substrate drugs of these CYP enzymes and transporters with narrow therapeutic index (including, but not limited to cyclosporine, paclitaxel and warfarin) should be avoided.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females and males

Women of childbearing potential should be informed that pralsetinib may cause foetal harm (see section 5.3).

The pregnancy status of women of childbearing potential should be verified prior to initiating Gavreto treatment.

Women of childbearing potential have to use highly effective non-hormonal contraception during treatment and for at least 2 weeks following the last dose of Gavreto (see section 4.4).

Males with female partners of childbearing potential have to use effective contraception during treatment with Gavreto and for at least 1 week following the last dose of Gavreto.

Patients should be advised to contact their healthcare provider immediately if they become pregnant, or if pregnancy is suspected, while taking Gavreto.

Pregnancy

There are no data from the use of pralsetinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Based on its mechanism of action and findings in animals, pralsetinib may cause foetal harm when administered to pregnant women.

Gavreto should not be used during pregnancy unless the clinical condition of the woman requires treatment with pralsetinib.

Breast-feeding

It is unknown whether pralsetinib or its metabolites are excreted in human milk.

A risk to the breast-fed child cannot be excluded.

Breast-feeding should be discontinued during treatment with Gavreto and for 1 week following the final dose.

Fertility

There is no clinical data on the effects of pralsetinib on fertility.
Based on non-clinical safety findings, fertility may be compromised during treatment with pralsetinib (see section 5.3). Men and women should seek advice on effective fertility preservation before treatment.

4.7 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 (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions were anaemia (47.2%), aspartate aminotransferase increased (46.0%), neutropenia (43.9%), constipation (41.9%), musculoskeletal pain (39.8%), fatigue (37.3%), leukopenia (35.4%), alanine aminotransferase increased (33.9%), and hypertension (33.0%). The most common serious adverse reactions were pneumonia (11.7%), pneumonitis (5.3%) and anaemia (3.8%).

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

Dose reductions due to adverse reactions occurred in 41.5% of patients treated with Gavreto. The most common adverse reactions resulting in dose reductions were neutropenia (14.0%), anaemia (8.5%), lymphopenia (5.3%), pneumonitis (5.3%), leukopenia (4.2%), blood creatine phosphokinase increased (4.0%), hypertension (4.0%), and fatigue (3.8%).

Permanent discontinuation due to adverse reactions occurred in 8.1% of patients treated with Gavreto. The most common adverse reactions that led to permanent discontinuation of Gavreto were pneumonia and pneumonitis (1.9% for each).

Tabulated list of adverse reactions

The safety population includes a total of 528 patients, including 281 patients with advanced NCSLC, as well as patients with other solid tumours (including RET fusion thyroid cancer and RET mutation medullary thyroid cancer), who received pralsetinib at a starting dose of 400 mg, see section 5.1. No clinically relevant differences in the safety profile across indications have been observed.

Adverse reactions reported in patients treated with Gavreto in the ARROW trial are listed below (Table 3), according to the MedDRA System Organ Class and frequency.

Frequencies are defined using 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 <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

Within each system organ class, adverse reactions are presented in order of decreasing frequency and severity.

Table 3. Adverse reactions reported in all patients treated with 400 mg Gavreto in the ARROW trial (N=528)

System organ class / Adverse reactions	**Frequency category**	**All grades %**	**Grades 3-4 %**
Infections and infestations			
Pneumonia[1]	Very common	17.4	10.2
Urinary tract infection		12.7	3.8
Blood and lymphatic system disorders			
Anaemia[2]	Very common	47.2	17.6
Neutropenia[3]		43.9	20.1
Leukopenia[4]		35.4	8.3
Lymphopenia[5]		22.3	14.2
Thrombocytopenia[6]		18.8	4.7
Metabolism and nutrition disorders			
Hypocalcaemia	Very common	20.6	3.6
Hyperphosphataemia		17.8	0.2
Hypoalbuminaemia		11.6	-
Hypophosphataemia		10.4	5.5
Hyponatraemia		10.2	4.2
Nervous system disorders			
Taste disorder[7]	Very common	15.9	-
Headache[8]		15.7	0.4
Vascular disorders			
Hypertension[9]	Very common	33.0	16.1
Haemorrhage[10]		18.8	3.0
Respiratory, thoracic and mediastinal disorders			
Cough[11]	Very common	23.7	0.6
Dyspnoea		16.9	2.1
Pneumonitis[12]		11.6	3.0
Gastrointestinal disorders			
Constipation	Very common	41.9	0.6
Diarrhoea		29.4	2.8
Dry mouth		15.9	-
Nausea		15.9	0.2
Abdominal pain[13]		15.3	1.3
Vomiting		12.3	1.1
Stomatitis[14]	Common	6.8	1.3

Hepatobiliary disorders			
Aspartate aminotransferase increased[*] Alanine aminotransferase increased[*] Hyperbilirubinaemia[15]	Very common	46.0 33.9 13.4	5.7 4.2 1.3
Skin and subcutaneous tissue disorders			
Rash[16]	Very common	17.2	-
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[17] Blood creatine phosphokinase increased	Very common	39.8 16.3	2.1 6.4
General disorders and administration site conditions			
Fatigue[18] Oedema[19] Pyrexia	Very common	37.3 28.2 25.2	4.0 0.2 1.1
Cardiac disorders			
QT prolongation[20]	Common	5.1	0.4
Renal and urinary disorders			
Blood creatinine increased	Very common	22.3	0.4

Investigations			
Blood alkaline phosphatase increased	Very common	10.4	1.1

[1] includes pneumonia, pneumocystis jirovecii pneumonia, pneumonia cytomegaloviral, atypical pneumonia, lung infection, pneumonia bacterial, pneumonia haemophilus, pneumonia influenzal, pneumonia streptococcal, pneumonia moraxella, pneumonia staphylococcal, pneumonia pseudomonal, atypical mycobacterial pneumonia, pneumonia legionella
[2] includes anaemia, haematocrit decreased, red blood cell count decreased, haemoglobin decreased, aplastic anaemia
[3] includes neutrophil count decreased, neutropenia
[4] includes white blood cell count decreased, leukopenia
[5] includes lymphopenia, lymphocyte count decreased
[6] includes thrombocytopenia, platelet count decreased
[7] includes ageusia, dysgeusia
[8] includes headache, tension headache
[9] includes hypertension, blood pressure increased
[10] includes 39 preferred terms from the SMQ Haemorrhage (excl laboratory terms) narrow, with the exclusion of terms related to invasive drug administration, terms related to rupture, disseminated intravascular coagulopathy, terms related to traumatic haemorrhages, and haemorrhagic terms related to pregnancy, birth or neonatal
[11] includes cough, productive cough
[12] includes pneumonitis, interstitial lung disease
[13] includes abdominal pain, abdominal pain upper
[14] includes stomatitis, aphthous ulcer
[15] includes blood bilirubin increased, hyperbilirubinaemia, bilirubin conjugated increased, blood bilirubin unconjugated increased
[16] includes rash, rash maculo-papular, dermatitis acneiform, erythema, rash generalised, rash papular, rash pustular, rash macular, rash erythematous
[17] includes musculoskeletal chest pain, myalgia, arthralgia, pain in extremity, neck pain, musculoskeletal pain, back pain, bone pain, spinal pain, musculoskeletal stiffness
[18] includes asthenia, fatigue
[19] includes oedema, swelling face, peripheral swelling, oedema peripheral, face oedema, periorbital oedema, eyelid oedema, generalised oedema, swelling, localised oedema
[20] includes electrocardiogram QT prolonged, long QT syndrome
[*] additionally, 3.0% transaminases increased were reported (0.6% Grades 3-4)

Description of selected adverse reactions

Pneumonitis/ILD

Pneumonitis and ILD occurred in 11.6% of 528 patients with NSCLC or other solid tumours, enrolled in the ARROW Study who received Gavreto (see section 4.4). Among the patients who had pneumonitis/ILD, the median time to onset was 15.6 weeks.

Serious adverse reactions of pneumonitis/ILD were reported for 5.3% of patients, including Grade 3 events (2.5%), Grade 4 (0.6%) and one fatal (Grade 5) event (0.2%).

In clinical trials, the majority of the patients with Grade 1 or Grade 2 pneumonitis were able to continue treatment without recurrent pneumonitis/ILD following dose interruption and dose reduction. Dose interruption occurred in 8.9%, dose reduction in 5.3% and permanent dose discontinuation in 1.9% of patients due to ILD/pneumonitis. The median time to resolution was 3.7 weeks.

Hypertension

Hypertension (including blood pressure increased) occurred in 33.0% of 528 patients with NSCLC or other solid tumours, including Grade ≤2 events in 16.9% and Grade 3 in 16.1% of patients. No Grade 4 or Grade 5 events were reported. Among the patients who had hypertension, the median time to onset was 2.1 weeks.

Serious adverse reactions of hypertension were reported in 1.3% of all patients (all Grade 3 events).

Dose interruption occurred in 7.4% of patients, dose reduction in 4.0% and one patient (0.2%) required permanent dose discontinuation. The median time to resolution was 3.1 weeks.

Transaminase elevations

Increased AST occurred in 46.0% of 528 patients, including Grade 3 or 4 in 5.7% of patients. Increased ALT occurred in 33.9% of patients, including Grade 3 or 4 events in 4.2% of patients. The median time to first onset for increased AST was 2.1 weeks and increased ALT was 3.1 weeks.

Serious adverse reactions of increased AST and ALT were each reported for 0.6% of all patients.

Dose interruption due to increased AST or ALT occurred in 4.4% and 3.4% of patients, respectively and dose reduction in 1.3% for both events. No patients required permanent dose discontinuation. The median time to resolution was 5.3 and 4.1 weeks for increased AST and ALT, respectively.

Haemorrhagic events

Haemorrhagic events occurred in 18.8% of the 528 patients, including Grade 3 events in 2.8% of patients and a Grade 4 or fatal (Grade 5) event each occurred in one patient (0.2%).

Serious adverse reactions of haemorrhage were reported for 3.2% of patients.

Fourteen patients (2.7%) required dose interruption and dose reduction or permanent dose discontinuation due to haemorrhage each occurred in one patient.

QT prolongation

QT prolongation occurred in 5.1% of 528 patients with NSCLC or other solid tumours. In 2 patients (0.4%) the event was assessed as serious. The majority of patients experienced non-severe events – i.e. Grade 1, in 21 (4.0%) and Grade 2, in 4 patients (0.8%). Two patients (0.4%) experienced Grade 3 events of Electrocardiogram QT prolonged, which both resolved. There was no life-threatening or fatal QT prolongation. Three patients (0.6%) had an event that remained unresolved by time of data cut-off. Dose reductions or interruptions were required by two Electrocardiogram QT prolonged patients, each. No QT prolongation event led to permanent discontinuation of pralsetinib.

Infections

Infections were commonly experienced by 57.2% of 528 patients during the median treatment time of 9.5 months. Most frequently (>10%), the preferred terms of pneumonia and urinary tract infection were reported (14.2% and 12.7%, respectively). The majority of infections were mild (Grade 1 or 2) and resolved; severe infection (Grade ≥3) occurred in 23.5% patients (with fatal events reported for 1.9%).

Infections reported as serious occurred for 24.2% of patients. The most common (>2%) serious infection preferred term was pneumonia (9.8%), followed by urinary tract infection (3.4%) and sepsis (2.8%). The majority of patients experiencing sepsis had concurrent pneumonia or urinary tract infection reported.

Dose interruption due to infection occurred for 19.5% of patients (mainly due to the preferred terms of pneumonia [6.8%] and urinary tract infection [2.7%]). Dose was reduced due to infections in 3.2% of patients (mainly due to the preferred term of pneumonia [1.9%]). Permanent treatment discontinuation was required by 3.4% of patients due to infections (mainly due to the preferred term of pneumonia [1.7%]).

Elderly

In ARROW (N=528), 37.8% of patients were 65 years of age and older. Compared with younger patients (<65), more patients of ≥65 years old reported adverse reactions that led to permanent dose discontinuation (25.8% versus 13.4%). Of the commonly reported events with higher incidence in elderly patients (≥65), hypertension has the greatest difference in comparison with patients <65 years of age. However, hypertension is also expected to occur more frequently in the elderly population. Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (87.1% versus 72.3%).

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. Healthcare professionals are asked to report any suspected adverse reactions via Roche Thailand Local Safety Unit at thailand.drug_safety@roche.com

4.9 Overdose

Symptoms

No cases of overdose have been reported in clinical trials with pralsetinib. The maximum dose of pralsetinib studied clinically is 600 mg orally once daily. Adverse reactions observed at this dose were consistent with the safety profile at 400 mg once daily (see section 4.8).

Management

There is no known antidote for Gavreto overdose. In the event of suspected overdose, Gavreto should be interrupted and supportive care instituted. Based on the large volume of distribution of pralsetinib and extensive protein binding, dialysis is unlikely to result in significant removal of pralsetinib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EX23.

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).

Pharmacodynamic effects

Cardiac electrophysiology

The QT interval prolongation potential of pralsetinib was assessed in 34 patients with RET fusion-positive solid tumours administered at 400 mg once daily in a formal ECG sub-study.

In patients receiving pralsetinib in the ARROW study, QT prolongation was reported (see section 4.8). Therefore, dose interruption or modification may be required in patients treated with pralsetinib (see sections 4.2 and 4.4).

Clinical efficacy and safety

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.

All NSCLC patients were required to have locally advanced or metastatic disease with measurable disease by Response Evaluable Criteria in Solid Tumours (RECIST) version 1.1. (v1.1) and have a RET fusion as determined by local testing (Next Generation Sequencing (NGS), fluorescence in situ hybridization (FISH), other). Patients with asymptomatic central nervous system (CNS) metastases, including patients with stable or decreasing steroid use within 2 weeks prior to study entry, were enrolled. The protocol excluded patients with a known primary driver alteration other than RET fusions, patients with a history of prolonged QT syndrome or Torsades de pointes or a familial history of prolonged QT syndrome, clinically symptomatic pneumonitis, and any prior or ongoing clinically significant medical condition that could affect patient's safety.

The primary efficacy outcome measure was overall response rate (ORR) according to RECIST v1.1 as evaluated by a Blinded Independent Central Review (BICR). Secondary efficacy outcomes included duration of response (DOR), progression free survival (PFS) and overall survival (OS).

Overall RET fusion-positive NSCLC population

The efficacy population consisted of 233 patients with RET fusion-positive advanced NSCLC who were treated at a starting dose of 400 mg orally once daily, including 75 who were treatment-naïve and 136 who previously received platinum-based chemotherapy. As of the last data cut-off date, the median follow-up was 17.1 months.

The demographic characteristics across the 233 patients were: 52.4% female, 51.9% White, 39.5% Asian, 3.9% Hispanic/Latino, and the median age was 60.0 years (range: 26 to 87) with 37.8% ≥65 years of age. The majority of patients had an ECOG performance status at baseline of 0 (33.5%) or 1 (63.9%), had metastatic disease (97.4%), had never smoked (62.2%) or were former smokers (33.5%) and had adenocarcinoma (96.1%). A history of brain metastases was seen in 37.3% of patients. Patients previously treated with platinum-based chemotherapy (N=136), received a median of 2 prior lines of therapy (range: 1-8). In addition to platinum-based chemotherapy, 40.4% received PD-1/PD-L1 inhibitors, 27.9% received multikinase inhibitors (MKIs) and 47.8% received prior radiation therapy. 21.3% of systemic treatment-naïve patients (N=75) received prior radiation therapy. RET fusions were detected in 79.4% of patients using NGS (42.9% tumour samples; 15.9% blood or plasma samples, 20.6% unknown), 18.0% using FISH, and 2.6% using other methods. The most common RET fusion partners were KIF5B (70.4%) and CCD6 (17.6%).

Efficacy results are summarised in Table 4. The median time to first response was 1.8 months for the overall population (range: 0.9-11.4 months), as well as for patients previously treated with platinum chemotherapy (range: 1.3-11.4 months) and treatment-naïve patients (range: 0.9-6.1 months).

Table 4: Efficacy results for RET fusion-positive advanced NSCLC (ARROW) (efficacy population)

Efficacy parameter	**Overall (N =233)**	**Previously treated with platinum chemotherapy (N=136)**	**Previously treated with non-platinum systemic treatment (N=22)**	**Treatment-naïve (N=75)**
Overall response rate (ORR)[a] (95% CI)	64.4% (57.9%, 70.5%)	58.8% (50.1%, 67.2%)	72.7% (49.8%, 89.3%)	72.0% (60.4%, 81.8%)
Complete response, n (%)	11 (4.7)	7 (5.1)	0	4 (5.3)
Partial response, n (%)	139 (59.7)	73 (53.7)	16 (72.7)	50 (66.7)
Duration of response (DOR)	**N=150**	**N=80**	**N=16**	**N=54**
DOR, median (95% CI) in months	22.3 (14.7, NR)	22.3 (15.1, NR)	NR (9.2, NR)	NR (9.0, NR)
Patients with DOR ≥ 6-months[b], %	68.0%	73.8%	81.3%	55.6%

NR= Not reached

[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

ORR and median DOR for the 233 patients with *RET* fusion-positive advanced NSCLC in the efficacy population was 64.4% (95% CI: 57.9, 70.5) and 22.3 months (95% CI: 14.7, NR), respectively.

No clinically relevant difference in efficacy was seen in patients with a KIF5B or CCDC6 fusion partner. BICR response rates were: ORR= 67.7% (95% CI: 59.9, 74.8) in 164 patients with a KIF5B fusion partner; and ORR= 68.3% (95% CI: 51.9, 81.9) in 41 patients with a CCDC6 fusion partner.

The intracranial ORR assessed by BICR was 70.0% (95% CI: 34.8, 93.3) in 10 response evaluable patients with brain metastases at baseline, including 3 patients with a complete response. All patients had target brain lesion shrinkage with pralsetinib treatment.

Elderly population

In ARROW (N=528), 37.8% of patients were 65 years of age and older. No overall differences in pharmacokinetic, safety or efficacy were observed in comparison with younger patients.

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 5.

Table 5: 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 6.

Table 6: 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)	NE (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 5.

Efficacy results for cabozantinib and vandetanib-naïve RET-mutant MTC are summarized in Table 7.

Table 7: 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

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 8.

Table 8: 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

5.2 Pharmacokinetic properties

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); pharmacokinetics was linear in the dose range of 200 and 400 mg in healthy volunteers. Pralsetinib plasma concentrations reached steady state by 3 to 5 days.

At the recommended dose of 400 mg once daily under fasting conditions, the mean steady state C_{max} of pralsetinib was 2830 ng/mL and the mean steady state area under the concentration-time curve (AUC_{0-24h}) was 43900 h•ng/mL. The mean accumulation ratio was ~2-fold after repeated dosing.

Absorption

The median time to peak concentration (T_{max}) ranged from 2.0 to 4.0 hours following single doses of pralsetinib 60 mg to 600 mg (0.15 to 1.5 times the approved recommended dose). The absolute bioavailability of pralsetinib has not been determined.

Effect of food
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) $AUC_{0-\infty}$ 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 apparent volume of distribution of pralsetinib is 3.8 L/kg (268 L). Plasma protein binding of pralsetinib is 97.1% and is independent of concentration. The blood-to-plasma ratio is 0.6 to 0.7.

Biotransformation

Pralsetinib is primarily metabolised by CYP3A4 and UGT1A4, and to a lesser extent by CYP2D6 and CYP1A2 *in vitro*.

Following a single oral dose of approximately 310 mg of radiolabelled pralsetinib to healthy subjects, pralsetinib metabolites from oxidation (M531, M453, M549b) and glucuronidation (M709) were detected in small to trace amounts (~ 5%).

Elimination

The mean plasma elimination half-life of pralsetinib was 14.7 hours following a single dose of 400 mg (the recommended dose) pralsetinib and 22.2 hours following multiple doses of 400 mg pralsetinib. The steady state mean apparent oral clearance of pralsetinib (CL/F) is 9.1 L/h.

Following a single oral dose of radiolabelled pralsetinib to healthy subjects, 72.5% of the radioactive dose was recovered in faeces (66% as unchanged) and 6.1% in urine (4.8% as unchanged).

Interactions with CYP substrates

In vitro studies indicate that pralsetinib is a time-dependent inhibitor of CYP3A4/5 at clinically relevant concentrations. Pralsetinib may have the potential to inhibit or induce CYP2C8, CYP2C9, and CYP3A4/5 at clinically relevant concentrations.

Interactions with transport proteins

In vitro studies indicate that pralsetinib may have the potential to inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1, and MATE2-K at clinically relevant concentrations. Pralsetinib is a substrate of P-gp. (see section 4.5).

In vitro studies with drug transporters

In vitro studies indicate that pralsetinib may be a potential substrate of P-glycoprotein (P-gp) and BCRP at clinically relevant concentrations.

Special populations

No clinically relevant differences in the pharmacokinetics of pralsetinib were observed based on age (19 to 87 years), sex, race (White, Black, or Asian), body weight (34.9 to 128 kg), mild to moderate (CL_{CR} 30 to 89 mL/min estimated by Cockcroft-Gault) renal impairment, or mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 times ULN and any AST). The effect of severe renal impairment (CL_{CR} 15 to 29 mL/min), end-stage renal disease (CL_{CR} < 15 mL/min), or moderate to severe hepatic impairment (total bilirubin > 1.5 times ULN and any AST) on the pharmacokinetics of pralsetinib is unknown (see section 4.2). Hence, no dose modifications are needed in the above mentioned special populations.

5.3 Preclinical safety data

Repeat-dose toxicity studies

In studies of up to 13 weeks duration in rats and cynomolgus monkeys, the primary findings at exposures similar to steady state human exposures (AUC) at 400 mg once daily in patients with advanced NSCLC included physeal dysplasia in the rat (2 times margin) and haematological effects (1 times margin) in both species. Additional adverse findings at higher exposures include degenerative changes in male and female reproductive organs (2 times margin) and increases in blood phosphorus with corresponding mineralization in soft tissues in rats (≥2 times margin), and myocardial haemorrhage in rats (4.4 times margin). Increased blood pressure was observed in rats after a single dose of 25 mg/kg (2 times). The No-Observed-Adverse-Effect-Level (NOAEL) of pralsetinib in the 13-week studies was 10 mg/kg/day in both species, corresponding to exposure (AUC) margins of 1 times relative to the human exposures.

Regarding local exposure and toxicity, there was no evidence of gastrointestinal disturbance in either species up to the NOAEL dose of 10 mg/kg (0.9 times human margin). At higher doses in monkeys, gastrointestinal ulcerations and haemorrhage were observed.

Embryotoxicity / Teratogenicity

In an embryo-fetal development study, administration of pralsetinib to rats during the period of organogenesis was teratogenic and embryotoxic at exposures below the steady-state human clinical exposure (AUC) at 400 mg once daily dose. Malformations, including visceral (primarily kidney and ureter) and skeletal (vertebral, rib, costal cartilage, and vertebral central anomalies) were observed at approximately 0.2-fold of the human exposure. Postimplantation loss occurred at 0.5-fold of the human exposure, and increased to 100% incidence at 1.5-fold of human exposure.

Reproductive toxicity

In a dedicated fertility and early embryonic development study conducted in treated male rats mated to treated female rats pralsetinib did not have an effect on male or female mating performance or ability to become pregnant. However, consistent with the findings of the embryofetal development toxicology study there was post-implantation loss at doses as low as 5 mg/kg (approximately 0.3 times the human exposure (AUC) at the clinical dose of 400 mg based on toxicokinetic data from the 13-week rat toxicology study). At the 20 mg/kg dose level (approximately 2.5-3.6 times the human exposure) 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 microscopic evidence of tubular degeneration/atrophy in the testis with secondary cellular debris and reduced sperm in the lumen of the epididymis, which correlated with lower mean testis and epididymis weights and gross observations of

soft and small testis. Female rats exhibited degeneration of the corpus luteum in the ovary. For both sexes, these effects were observed at pralsetinib doses ≥10 mg/kg/day, approximately 0.9 times the human exposure based on AUC at the clinical dose of 400 mg.
No findings were noted in the reproductive organs in a 13-week repeated-dose toxicology study in monkeys at dose levels up to 10 mg/kg/day (approximately 1 times the human exposure at the 400 mg once daily dose).

Genotoxicity and carcinogenicity

Pralsetinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay and was negative in both *in vitro* human lymphocyte chromosome aberration assay and *in vivo* rat bone marrow micronucleus tests.

Carcinogenicity studies with pralsetinib have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Hydroxypropyl Methylcellulose
Cellulose microcrystalline
Starch, pregelatinised
Sodium hydrogen carbonate
Citric acid
Magnesium stearate

Capsule shell

Brilliant blue FCF (E133)
Hypromellose
Titanium dioxide (E171)

Printing ink

Shellac
Propylene glycol (E1520)
Potassium hydroxide
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with child-resistant closure (polypropylene) and foiled induction seal liner and desiccant sachet (silica gel)

Pack sizes: 60, 90 or 120 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Imported by Roche Thailand Ltd., Bangkok

8. MARKETING AUTHORISATION NUMBER(S)

See on package

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: See on product license

10. DATE OF REVISION OF THE TEXT

Current at April 2022