ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 (22 mm long x 7 mm wide) 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

Gavreto is indicated as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor.

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 fusion-positive advanced NSCLC 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.
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 cytochrome P-450 (CYP)3A4 and/or P-glycoprotein (P-gp) inhibitors
Concomitant use of pralsetinib with any of the following should be avoided (see section 4.4 and section 4.5):

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

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

If co-administration with any of the above inhibitors cannot be avoided, the current dose of pralsetinib should be reduced as recommended in Table 2. After the co-administered inhibitor has been discontinued for 3 to 5 elimination half-lives of the inhibitor, 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 CYP3A4 and/or P-gp inhibitors

Current Gavreto dose	**Recommended Gavreto dose**	
	Combined P-gp and strong CYP3A4 inhibitors	• **Strong CYP3A4 inhibitors;** • **Moderate CYP3A4 inhibitors;** • **P-gp inhibitors;** • **Combined P-gp and moderate CYP3A4 inhibitors**
400 mg orally once daily	200 mg orally once daily	300 mg orally once daily
300 mg orally once daily	200 mg orally once daily	200 mg orally once daily
200 mg orally once daily	100 mg orally once daily	100 mg orally once daily

Dose modification for use with CYP3A4 inducers
Concomitant use of pralsetinib with strong or moderate CYP3A4 inducers should be avoided (see section 4.4 and section 4.5).

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 (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or total bilirubin > 1 to 1.5 times ULN and any AST), moderate (total bilirubin > 1.5 to 3 times ULN and any AST) or severe hepatic impairment (total bilirubin > 3 times ULN and any AST) (see section 5.2).

Elderly

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

Paediatric population

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.

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).

Tuberculosis

Tuberculosis, mostly extrapulmonary, has been reported in patients receiving Gavreto. Before starting treatment, patients should be evaluated for active and inactive ("latent") tuberculosis, as per local recommendations. In patients with active or latent tuberculosis, standard antimycobacterial therapy should be initiated before treatment with Gavreto is started.

Drug interactions

Co-administration of Gavreto with combined P-gp inhibitors and strong CYP3A4 inhibitors, P-gp inhibitors, strong or moderate CYP3A4 inhibitors or combined P-gp and moderate 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 or moderate 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, including a barrier method (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

CYP3A4 and/or P-gp inhibitors
P-gp inhibitors: Co-administration of a single 200 mg dose of pralsetinib with cyclosporine single 600 mg dose (a P-gp and weak-moderate CYP3A4 inhibitor) in healthy subjects increased pralsetinib $AUC_{0-\infty}$ by 81% and C_{max} by 48%, relative to a 200 mg dose of pralsetinib administered alone.

Combined P-gp and strong CYP3A4 inhibitors: Co-administration of 200 mg pralsetinib once daily with itraconazole 200 mg once daily (a P-gp inhibitor and strong CYP3A4) increased pralsetinib $AUC_{0-\infty}$ by 251% and C_{max} by 84% , compared to pralsetinib administered alone.

Co-administration of pralsetinib with P-gp and/or strong or moderate CYP3A4 inhibitors may increase pralsetinib plasma concentrations, which may increase the risk of adverse reactions of pralsetinib. Co-administration of pralsetinib with the following should be avoided (see section 4.4):

- combined P-gp and strong CYP3A4 inhibitors (including, but not limited to, ketoconazole, itraconazole, cobicistat, clarithromycin, ritonavir, or saquinavir)
- strong CYP3A4 inhibitors (including, but not limited to, telithromycin, troleandomycin, voriconazole, ceritinib, idelalisib, nefazodone, nelfinavir, or grapefruit juice)
- moderate CYP3A4 inhibitors (including, but not limited to, aprepitant, ciprofloxacin, conivaptan, crizotinib, fluconazole, fluvoxamine, imatinib, isavuconazole, or tofisopam)
- P-gp inhibitors (including, but not limited to, cyclosporine, carvedilol or quinidine)
- combined P-gp and moderate CYP3A4 inhibitors (including, but not limited to, dronedarone, diltiazem, erythromycin, verapamil)

If co-administration with any of the above 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 $AUC_{0-\infty}$ by 68% and C_{max} by 30%. Therefore, co-administration of pralsetinib with strong CYP3A4 inducers (including, but not limited to, carbamazepine, phenytoin, rifabutin, rifampicin and St. John's Wort [*Hypericum perforatum*]) should be avoided (see section 4.4).

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 must use effective contraception, including a barrier method, 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 (53.0%), aspartate aminotransferase increased (49.1%), neutropenia (46.7%), musculoskeletal pain (44.4%), constipation (43.9%), fatigue (42.2%), alanine aminotransferase increased (37.0%), leukopenia (37.0%), and hypertension (35.0%).

The most common serious adverse reactions were pneumonia (15.6%), pneumonitis (5.7%) and anaemia (5.2%).

The most common severe adverse reactions were anaemia (22.4%), neutropenia (21.1%), hypertension (17.6%), pneumonia (15.4%), and lymphopenia (17.4%).

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 46.7% of patients treated with Gavreto. The most common adverse reactions resulting in dose reductions were neutropenia (15.6%), anaemia (10.6%), lymphopenia (7.2%), pneumonitis (5.7%), blood creatine phosphokinase increased (5.2%), hypertension (4.8%), leukopenia (4.6%), and fatigue (4.1%).

Permanent discontinuation due to adverse reactions occurred in 10.6% of patients treated with Gavreto. The most common adverse reactions that led to permanent discontinuation of Gavreto were pneumonia and pneumonitis (2.6% and 2.2%, respectively).

Tabulated list of adverse reactions

The safety population includes a total of 540 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=540)

System organ class / Adverse reactions	**Frequency category**	**All grades %**	**Grades 3-4 %**
Infections and infestations			
Pneumonia[1]	Very common	22.4	13.1
Urinary tract infection		14.8	4.4
Tuberculosis[2]	Uncommon	0.7	0.4
Blood and lymphatic system disorders			
Anaemia[3]	Very common	53.0	22.4
Neutropenia[4]		46.7	21.1
Leukopenia[5]		37.0	8.9
Lymphopenia[6]		26.9	17.4
Thrombocytopenia[7]		19.6	4.8
Metabolism and nutrition disorders			
Hypocalcaemia	Very common	23.1	3.9
Hyperphosphataemia		17.4	0.2
Hypoalbuminaemia		14.8	-
Hypophosphataemia		13.0	6.7
Hyponatraemia		12.2	4.4
Nervous system disorders			
Headache[8]	Very common	18.0	0.6
Taste disorder[9]		16.7	-
Vascular disorders			
Hypertension[10]	Very common	35.0	17.6
Haemorrhage[11]		20.6	3.9
Respiratory, thoracic and mediastinal disorders			
Cough[12]	Very common	28.1	0.6
Dyspnoea		20.4	2.0
Pneumonitis[13]		12.2	3.3
Gastrointestinal disorders			
Constipation	Very common	43.9	0.6
Diarrhoea		33.1	3.1
Nausea		19.6	0.2
Abdominal pain[14]		17.8	1.5
Dry mouth		16.5	-
Vomiting		14.8	1.1
Stomatitis[15]	Common	6.9	1.3
Hepatobiliary disorders			
Aspartate aminotransferase increased*	Very common	49.1	6.9
Alanine aminotransferase increased*		37.0	4.8
Hyperbilirubinaemia[16]		14.4	1.7
Skin and subcutaneous tissue disorders			
Rash[17]	Very common	19.1	-
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[18]	Very common	44.4	2.6
Blood creatine phosphokinase increased		16.7	7.6
General disorders and administration site conditions			
Fatigue[19]	Very common	42.2	4.1
Oedema[20]		31.5	0.2
Pyrexia		27.8	1.5
Cardiac disorders			
QT prolongation[21]	Common	5.2	0.4

Renal and urinary disorders			
Blood creatinine increased	Very common	25.4	0.6
Investigations			
Blood alkaline phosphatase increased	Very common	12.0	1.5

[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] most of the cases reported extrapulmonary tuberculosis such as lymph node tuberculosis, peritoneal tuberculosis or renal tuberculosis
[3] includes anaemia, haematocrit decreased, red blood cell count decreased, haemoglobin decreased, aplastic anaemia
[4] includes neutrophil count decreased, neutropenia
[5] includes white blood cell count decreased, leukopenia
[6] includes lymphopenia, lymphocyte count decreased
[7] includes thrombocytopenia, platelet count decreased
[8] includes headache, tension headache
[9] includes ageusia, dysgeusia
[10] includes hypertension, blood pressure increased
[11] 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
[12] includes cough, productive cough
[13] includes pneumonitis, interstitial lung disease
[14] includes abdominal pain, abdominal pain upper
[15] includes stomatitis, aphthous ulcer
[16] includes blood bilirubin increased, hyperbilirubinaemia, bilirubin conjugated increased, blood bilirubin unconjugated increased
[17] includes rash, rash maculo-papular, dermatitis acneiform, erythema, rash generalised, rash papular, rash pustular, rash macular, rash erythematous
[18] includes musculoskeletal chest pain, myalgia, arthralgia, pain in extremity, neck pain, musculoskeletal pain, back pain, bone pain, spinal pain, musculoskeletal stiffness
[19] includes asthenia, fatigue
[20] includes oedema, swelling face, peripheral swelling, oedema peripheral, face oedema, periorbital oedema, eyelid oedema, generalised oedema, swelling, localised oedema
[21] includes electrocardiogram QT prolonged, long QT syndrome
[*] additionally, transaminases increased were reported in 3.7% (0.6% Grades 3-4)

Description of selected adverse reactions

Pneumonitis/ILD

Pneumonitis and ILD occurred in 12.2% of 540 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 16.1 weeks.

Serious adverse reactions of pneumonitis/ILD were reported for 5.7% of patients, including Grade 3 events (2.8%), 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 5.7% and permanent dose discontinuation in 2.2% of patients due to ILD/pneumonitis. The median time to resolution was 4.3 weeks.

Hypertension

Hypertension (including blood pressure increased) occurred in 35.0% of 540 patients with NSCLC or other solid tumours, including Grade ≤2 events in 17.4% and Grade 3 in 17.6% 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 8.0% of patients, dose reduction in 4.8% and one patient (0.2%) required permanent dose discontinuation. The median time to resolution was 4.0 weeks.

Transaminase elevations

Increased AST occurred in 49.1% of 540 patients, including Grade 3 or 4 in 6.9% of patients. Increased ALT occurred in 37.0% of patients, including Grade 3 or 4 events in 4.8% of patients. The median time to first onset for increased AST was 2.1 weeks and increased ALT was 3.5 weeks.

Serious adverse reactions of increased AST and ALT were reported in 0.7% and 0.6% of patients, respectively.

Dose interruption due to increased AST or ALT occurred in 5.0% and 3.9% of patients, respectively and dose reduction in 2.0% and 1.5%, respectively. No patients required permanent dose discontinuation. The median time to resolution was 6.0 and 5.1 weeks for increased AST and ALT, respectively.

Haemorrhagic events

Haemorrhagic events occurred in 20.6% of the 540 patients, including Grade 3 events in 3.7% 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 3.9% of patients.

Seventeen patients (3.1%) required dose interruption. Dose reduction or permanent dose discontinuation due to haemorrhage occurred in 0.4% and 0.2% of patients, respectively.

QT prolongation

QT prolongation occurred in 5.2% of 540 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 (3.9%) and Grade 2, in 5 patients (0.9%). 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 66.1% of 540 patients during the median treatment time of 15.9 months. Most frequently (>10%), pneumonia and urinary tract infection were reported (22.4% and 14.8%, respectively). The majority of infections were mild (Grade 1 or 2) and resolved; severe infection (Grade ≥3) occurred in 30.4% patients (with fatal events reported for 4.1%).

Infections reported as serious occurred for 18.5% of patients. The most common (>2%) serious infection was pneumonia (15.6%), followed by urinary tract infection (3.7%) and sepsis (3.7%). The majority of patients experiencing sepsis had concurrent pneumonia or urinary tract infection reported.

Dose interruption due to infection occurred in 12.8% of patients (mainly due to pneumonia [10.9%] and urinary tract infection [2.6%]). Dose was reduced due to infections in 3.7% of patients (mainly due to pneumonia [3.5%]). Permanent treatment discontinuation was required by 2.6% of patients due to infections (mainly due to pneumonia [2.6%]).

Elderly

In ARROW (N=540), 30.9% 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 (29.3% versus 18.8%). 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 (89.8% versus 78.3%).

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 the national reporting system listed in Appendix V.

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 potent protein kinase inhibitor that selectively targets oncogenic RET fusions (KIF5B-RET and CCDC6-RET). In NSCLC, RET fusions are one of the main oncogenic drivers. *In vitro*, pralsetinib inhibited several oncogenic RET fusions more potently than off-target kinases at clinically relevant concentrations (e.g. 81-fold selectivity over VEGFR2). Pralsetinib exhibited anti-tumour activity in cultured cells and animal tumour implantation models representing multiple tumour types harbouring oncogenic RET fusions (KIF5B-RET, CCDC6-RET).

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 studied in patients with RET fusion-positive advanced NSCLC in Study BLU-667-1101 (ARROW), a multicenter, non-randomised, open-label, multi-cohort phase I/II clinical trial. The study enrolled, in separate cohorts, patients with RET fusion-positive advanced NSCLC who had progressed on platinum-based chemotherapy as well as patients that progressed on prior therapy other than platinum based therapy or were systemic treatment-naïve. The study was ongoing at the time of approval.

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 281 patients with RET fusion-positive advanced NSCLC who were treated at a starting dose of 400 mg orally once daily, including 116 who were treatment-naïve and 141 who previously received platinum-based chemotherapy. As of the last data cut-off date (4 March 2022), the median follow-up was 24.1 months.

The demographic characteristics across the 281 patients were: 54.1% female, 46.3% White, 45.6% Asian, 3.6% Hispanic/Latino, and the median age was 60.0 years (range: 26 to 87) with 37.4% ≥65 years of age. The majority of patients had an ECOG performance status at baseline of 0 (29.5%) or 1 (68.0%), had metastatic disease (98.6%), had never smoked (62.6%) or were former smokers (33.1%) and had adenocarcinoma (96.8%). A history of brain metastases was seen in 34.5% of patients. Patients previously treated with platinum-based chemotherapy (N=141), 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, 27.7% received multikinase inhibitors (MKIs) and 48.9% received prior radiation therapy. 15.5% of systemic treatment-naïve patients (N=116) received prior radiation therapy. RET fusions were detected in 75.8% of patients using NGS (36.7% tissue samples; 15.7% plasma samples, 23.5% unknown), 15.3% using FISH, 6.0% unknown, and 2.8% using other methods. The most common RET fusion partners were KIF5B (70.1%) and CCD6 (17.8%).

Efficacy results are summarised in Table 4. The median time to first response was 1.8 months for the overall population (range: 0.9-20.5 months), as well as for patients previously treated with platinum chemotherapy (range: 1.3-11.4 months) and treatment-naïve patients (range: 0.9-20.5 months).

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

Efficacy parameter	**Overall (N =281)**	**Previously treated with platinum chemotherapy (N=141)**	**Previously treated with non-platinum systemic treatment (N=24)**	**Treatment-naive (N=116)**
Overall response rate (ORR)[a] (95% CI)	65.8% (60.0%, 71.4%)	59.6% (51.0%, 67.7%)	70.8% (48.9%, 87.4%)	72.4% (63.3%, 80.3%)
Complete response, n (%)	18 (6.4)	10 (7.1)	0	8 (6.9)
Partial response, n (%)	167 (59.4)	74 (52.5)	17 (70.8)	76 (65.5)
Duration of response (DOR)	**N=185**	**N=84**	**N=17**	**N=84**
DOR, median (95% CI) in months	19.1 (14.5, 27.3)	23.4 (14.8, 39.4)	20.4 (9.3, NR)	13.4 (9.4, 23.1)
Patients with DOR ≥ 6-months[b], %	79.5%	81.0%	94.1%	75.0%

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

No clinically relevant difference in efficacy was seen in patients with a KIF5B or CCDC6 fusion partner. BICR response rates were: ORR= 68.5% (95% CI: 61.5, 74.9) in 197 patients with a KIF5B fusion partner; and ORR= 72.0% (95% CI: 57.5, 83.8) in 50 patients with a CCDC6 fusion partner.

In the efficacy population, the CNS ORR by central assessment (per RECIST v1.1) was 53.3% (95% CI: 26.6, 78.7); 3 patients (20.0%) had a CR and 5 patients (33.3%) had a PR.

Elderly population

In ARROW (N=540), 30.9% of patients were 65 years of age and older. No overall differences in pharmacokinetic, safety or efficacy were observed in comparison with younger patients.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Gavreto in all subsets of the paediatric population in the treatment of lung cancer (small cell and non-small cell lung cancer) (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Pralsetinib C_{max} and AUC in patients 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 2840 ng/mL and the mean steady state area under the concentration-time curve (AUC_{0-24h}) was 40100 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 steady state mean apparent volume of distribution of pralsetinib is 255 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 13.4 hours following a single dose of 400 mg (the recommended dose) pralsetinib and 17.9 hours following multiple doses of 400 mg pralsetinib. The steady state mean apparent oral clearance of pralsetinib (CL/F) is 9.9 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).

In vitro studies 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.

In vitro studies with drug transporters

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. *In vitro* studies also

indicate that pralsetinib may be a potential substrate of P-gp at clinically relevant concentrations (see section 4.5).

Special populations

Based on the population PK model, 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 hepatic impairment, or mild to moderate renal impairment (CL_{CR} 30 to 89 mL/min estimated by Cockcroft-Gault). Hence, no dose modifications are needed in the above-mentioned special populations. The effect of severe renal impairment (CL_{CR} 15 to 29 mL/min), end-stage renal disease (CL_{CR} < 15 mL/min) on the pharmacokinetics of pralsetinib is unknown (see section 4.2).

Hepatic Impairment
Following a single oral dose of 200 mg pralsetinib, peak pralsetinib exposure was similar in subjects with moderate hepatic impairment (as defined by Child-Pugh criteria) compared to subjects with normal hepatic function, with geometric mean ratios (GMR) (90% CI) of 98.6% (59.7, 163) for C_{max} and 112% (65.4, 193) for $AUC_{0-\infty}$. In subjects with severe hepatic impairment (as defined by Child-Pugh criteria), $AUC_{0-\infty}$ was also similar compared to subjects with normal hepatic function (85.8% [51.1, 144]). C_{max} was slightly lower in subjects with severe hepatic impairment compared to subjects with normal hepatic function, with a C_{max} GMR of 67.9% (35.3, 131). Unbound C_{max} ($C_{max,u}$) and $AUC_{0-\infty}$ ($AUC_{0-\infty,u}$) were slightly higher in subjects with severe hepatic impairment (as defined by Child-Pugh criteria) compared to subjects with normal hepatic function, with a $C_{max,u}$ GMR of 129% (70.4, 236) and $AUC_{0-\infty,u}$ GMR of 163% (98.7, 268). There was no clear relationship between C_{max} or $AUC_{0-\infty}$ and Child-Pugh total score or the components of the Child-Pugh score. Similar PK results were obtained when hepatic impairment subjects were classified by NCI-ODWG criteria.

Therefore, no dose adjustment is needed in patients with hepatic impairment.

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 separate fertility and early embryonic development study in which male rats administered pralsetinib were mated with untreated female rats, intrauterine survival of the embryos (mean litter proportions of post-implantation loss and mean numbers and litter proportions of viable embryos) were unaffected by pralsetinib administration to males at the 20 mg/kg dose level (approximately 1.4 times the human exposure (AUC) at the clinical dose of 400 mg based on toxicokinetic data collected in this study). In addition, no pralsetinib-related effects on male reproductive performance (mating, fertility, and pregnancy indices) were observed in this study.

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

Hypromellose
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

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
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

Blueprint Medicines (Netherlands) B.V.
Gustav Mahlerplein 2
1082 MA Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1555/001
EU/1/21/1555/002
EU/1/21/1555/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 November 2021
Date of latest renewal: 15 September 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the efficacy and safety of pralsetinib in the treatment of adult patients with RET fusion-positive advanced NSCLC, the MAH should submit the results of study BLU-667-2303, a randomised, open-label, Phase 3 Study of pralsetinib versus standard of care for first line treatment of RET fusion-positive, metastatic NSCLC.	31 December 2026

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Gavreto 100 mg hard capsules
pralsetinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 100 mg of pralsetinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules
90 hard capsules
120 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant sachet found in the bottle

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Blueprint Medicines (Netherlands) B.V.
Gustav Mahlerplein 2
1082 MA Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1555/001 60 hard capsules
EU/1/21/1555/002 90 hard capsules
EU/1/21/1555/003 120 hard capsules

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

gavreto 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Gavreto 100 mg hard capsules
pralsetinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 100 mg of pralsetinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules
90 hard capsules
120 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant sachet found in the bottle

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Blueprint Medicines (Netherlands) B.V. logo

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1555/001 60 hard capsules
EU/1/21/1555/002 90 hard capsules
EU/1/21/1555/003 120 hard capsules

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Gavreto 100 mg hard capsules
pralsetinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Gavreto is and what it is used for

What Gavreto is

Gavreto is a cancer medicine that contains the active substance pralsetinib.

What Gavreto is used for

Gavreto is used to treat adults with advanced stages of a form of lung cancer called 'non-small cell lung cancer' ('NSCLC'), that presents with a specific rearrangement in a gene called rearranged during transfection (RET) if you have not been previously treated with another RET inhibitor medicine.

How Gavreto works

In patients whose cancer is due to an altered RET gene, the change in the gene causes the body to make an abnormal protein called a RET fusion protein, which can lead to uncontrolled cell growth and cancer. Gavreto blocks the action of RET fusion proteins and may help to slow or stop your lung cancer from growing. It may also help to shrink your cancer.

If you have any questions about how Gavreto works or why this medicine has been prescribed for you, please ask your doctor.

2. What you need to know before you take Gavreto

Do not take Gavreto

- if you are allergic to pralsetinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking Gavreto.
- if you have a history of lung or breathing problems other than lung cancer.
- if you have had high blood pressure
- if you have had liver problems
- if you have had bleeding problems
- if you have ever had tuberculosis or if you have been in close contact with someone who has or has had tuberculosis. Your doctor may perform tests to see if you have tuberculosis

Gavreto can cause side effects that you need to tell your doctor about straight away. These include:
- **lung inflammation (pneumonitis).** Gavreto may cause severe, life-threatening or fatal swelling (inflammation) of the lungs during treatment. The signs may be similar to those from your lung cancer. Tell your doctor straight away if you have any new or worsening signs including difficulty in breathing, shortness of breath, or cough with or without mucous, or fever.
- **high blood pressure (hypertension)**. Gavreto can increase the occurrence of high blood pressure. Your doctor will monitor your blood pressure before you start treatment, then after 1 week of your treatment and then as needed. If you have high blood pressure which is not well controlled with blood pressure medicines, please consult your doctor as it is important to make sure that your blood pressure is under control before starting Gavreto treatment.
- **liver injury (transaminase elevations)**. Your doctor will take blood tests before you start treatment, then every 2 weeks for the first 3 months of your treatment and then as needed. This is to check you do not have any liver problems while taking Gavreto. Tell your doctor straight away if you get any of the following signs: yellowing of your skin or the whites of your eyes, pain on the right side of your stomach area, dark urine, itchy skin, feeling less hungry than usual, nausea or vomiting, feeling tired, bleeding or bruising more easily than normal.
- **bleeding problems.** Serious bleeding can occur during treatment with Gavreto. Tell your doctor straight away if you have any of these symptoms: are vomiting blood or vomit that looks like coffee-grounds, coughing up blood or blood clots, have pink or brown urine, red or black (looks like tar) stools, unusual bleeding or bruising of your skin, menstrual bleeding that is heavier than normal, unusual vaginal bleeding, nose bleeds that happen often, drowsiness or difficulty being awakened.
- **abnormal ECG.** Gavreto may result in abnormal ECGs. You will have an ECG taken before and during your treatment with Gavreto. Tell your Doctor if you feel light-headed or experience palpitations as it may be a symptom of abnormal ECG.

Look out for this while you are taking Gavreto. See ‘Side effects’ in section 4 for more information.

Children and adolescents

Gavreto has not been studied in children or adolescents. Do not give this medicine to children or adolescents under the age of 18 years.

Other medicines and Gavreto

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Gavreto may affect the way other medicines work, and certain other medicines may affect how Gavreto works.

Tell your doctor or pharmacist before taking Gavreto if you are taking any of the following medicines:

The following medicines can increase the concentration of Gavreto in the blood:
- certain medicines used to treat AIDS/HIV (e.g. ritonavir, saquinavir, cobicistat)
- certain medicines used to treat infections. These include medicines that treat fungal infections (antifungals such as ketoconazole, itraconazole, voriconazole, posaconazole) and medicines that treat certain types of bacterial infection (antibiotics such as clarithromycin, erythromycin)
- certain medicines used to treat depression (e.g. fluvoxamine, nefazodone)
- certain medicines used to treat high blood pressure and irregular heart rhythms (e.g. verapamil, diltiazem)

The following medicines can reduce the effectiveness of Gavreto:
- medicines used to stop seizures or fits (anti-epileptics such as phenytoin or carbamazepine)
- medicines used to treat tuberculosis (e.g. rifampicin, rifabutin)
- St. John's Wort, a herbal medicine used to treat depression

Gavreto may affect the way some other medicines work, including:
- cyclosporine
- paclitaxel
- warfarin

The medicines listed here may not be the only ones that could interact with Gavreto.

Ask your doctor or pharmacist for advice before taking any medicine.

Gavreto with food and drink

You should avoid drinking grapefruit juice and eating grapefruit or Seville oranges while on treatment with Gavreto.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Contraception in females:

You should avoid becoming pregnant while taking this medicine. If you are able to have children, you must use highly effective contraception (for example, double-barrier contraception such as condom and diaphragm) while on treatment and for at least 2 weeks after stopping treatment. Gavreto may reduce the effectiveness of hormonal contraceptive methods (for example, birth control pill); therefore, hormonal contraceptives may not be considered highly effective. If hormonal contraception is unavoidable, it must be used in combination with a condom.

Contraception in males:

Males with female partners of childbearing potential must use effective contraception, including a barrier method, during treatment and for 1 week after completion of treatment.

Talk to your doctor about the right methods of contraception for you and your partner.

Pregnancy:

This medicine is not recommended for use during pregnancy unless absolutely necessary. Avoid becoming pregnant while being treated with this medicine as it may harm your unborn baby. Your doctor will discuss with you the potential risks of taking Gavreto during pregnancy.

Your doctor may check if you are pregnant before you start treatment with this medicine.

Breast-feeding:

Tell your doctor if you are breast-feeding or planning to breast-feed. It is not known if Gavreto passes into your breast milk. You should not breast-feed during treatment with this medicine and for at least 1 week after the last dose. Talk to your doctor about the best way to feed your baby during this time.

Fertility:

It is possible that this medicine could permanently affect your ability to have children. You are encouraged to talk to a doctor about saving your sperm or eggs before using Gavreto.

Driving and using machines

Gavreto may affect your ability to drive or use machines. Gavreto may cause you to feel fatigued. If this happens, you should not drive or operate heavy machinery until your symptoms resolve. Talk to your doctor about whether it is okay for you to drive or use machines.

Gavreto contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially "sodium-free".

3. How to take Gavreto

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is 400 mg (4 capsules) taken by mouth once daily.

If you get side-effects, your doctor may change your dose, temporarily stop, or permanently stop treatment. Do not change your dose or stop taking Gavreto unless your doctor tells you to.

Gavreto is for oral use. Swallow the capsules whole with a glass of water, on an empty stomach. Do not eat for at least two hours before and at least one hour after taking Gavreto.

If you vomit after taking a dose of Gavreto, do not take an extra dose. Take your regular dose of Gavreto the next day.

If you take more Gavreto than you should

If you have accidentally taken too many capsules, talk to your doctor straight away. You may require medical attention.

If you forget to take Gavreto

If you miss a dose of Gavreto, take it as soon as you remember on the same day. Take your regular dose of Gavreto the next day.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects

Some side effects may be serious. Tell your doctor straight away if you get the following side effect (see also section 2):

- New or worsening signs of difficulty in breathing, shortness of breath, or cough with or without mucous, or fever
- High blood pressure.
- Yellowing of your skin or the whites of your eyes, pain on the right side of your stomach area, dark urine, itchy skin, feeling less hungry than usual, nausea or vomiting, feeling tired, bleeding or bruising more easily than normal (potential signs of liver problems).
- Bleeding with symptoms such as coughing up blood

Other side effects:

Tell your doctor or pharmacist if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people):

- Lung infection
- Bladder infection
- Blood test showing decrease in red blood cells
- Blood test showing decrease in a type of white blood cells (e.g., neutrophils, lymphocytes, etc.)
- Low platelet level
- Blood tests showing increased or decreased amounts of blood mineral
- Altered taste
- Headache
- Increased blood pressure
- Bleeding
- Lung inflammation
- Cough
- Shortness of breath
- Constipation
- Diarrhoea
- Dryness affecting eyes, mouth and skin
- Abdominal (belly) pain
- Vomiting
- Yellow skin and eyes
- Rash
- Bone or muscle pain
- Lack of energy
- Swellings (e.g. feet, ankle, face, eye, joint)
- Fever
- Blood tests showing altered amounts of a substance produced by the liver (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin)
- Blood test showing an increased level of an important substance used for assessing kidney function (creatinine)
- Blood test showing higher amounts of an enzyme important for muscle function in your blood (creatine phosphokinase)

Common (may affect up to 1 in 10 people):
- Painful swelling and sores in the mouth
- Prolongation of the QT interval on your ECG

Uncommon (may affect up to 1 in 100 people):
- Tuberculosis

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Gavreto

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and outer carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.

Do not use this medicine if you notice that the bottle is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Gavreto contains

- The active substance is pralsetinib. Each hard capsule contains 100 mg of pralsetinib.
- The other ingredients are:
  - The capsule content contains: hypromellose, microcrystalline cellulose, pregelatinised starch, sodium hydrogen carbonate, citric acid, and magnesium stearate (see section 2 "Gavreto contains sodium").
  - The capsule shell contains: brilliant blue FCF (E133), hypromellose, and titanium dioxide (E171).
  - The printing ink contains: shellac, propylene glycol (E1520), potassium hydroxide, and titanium dioxide (E171).

What Gavreto looks like and contents of the pack

Gavreto 100 mg hard capsules are light blue, opaque hard capsules with "BLU-667" printed on the capsule shell body and "100 mg" on the capsule shell cap in white ink.

Gavreto is available in a plastic bottle with child-resistant closure containing 60, 90 or 120 hard capsules and a desiccant sachet. Each carton contains one bottle.

Keep the desiccant sachet in the bottle. The desiccant is a moisture absorbing material filled in a small sachet to protect the capsules from moisture. Do not swallow the desiccant.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Manufacturer

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This leaflet was last revised in.

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu