▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
GAVRETO® (pralsetinib)

1. GAVRETO
Pralsetinib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each hard capsule contains 100 mg pralsetinib.

Gavreto (pralsetinib) 100 mg, light blue, opaque, immediate release, hydroxypropyl methylcellulose (HPMC) hard capsule printed with "BLU-667" on the capsule shell body and "100 mg" on the capsule shell cap.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM
Hard capsule.

Gavreto is a size 0 capsule with light blue body and cap and BLU-667 imprinted in white on the body.

4. CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS

Non-Small Cell Lung Cancer (NSCLC)
Gavreto has **provisional approval** in Australia for the treatment of adult patients with locally advanced or metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC). The decision to approve this indication has been made on the basis of overall response rate (ORR) and duration of response (DOR) in single-arm trials. Continued approval of this indication depends on verification and description of benefit in confirmatory trials.

RET-Fusion Positive Thyroid Cancer
Gavreto has **provisional approval** in Australia for the treatment of adult patients with advanced or metastatic RET-fusion positive thyroid cancer that is refractory to (or unsuitable for) radioactive iodine and who have progressed on or are unable to tolerate lenvatinib or sorafenib. The decision to approve this indication has been made on the basis of overall response rate (ORR) and duration of response (DOR). Continued approval of this indication depends on verification and description of benefit in confirmatory trials.

4.2 DOSE AND METHOD OF ADMINISTRATION

General

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

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

Patient selection

NSCLC and RTC
A validated assay is required for the selection of patients with RET-fusion positive locally advanced or metastatic NSCLC; or for RET-fusion positive Thyroid cancer. RET-fusion status should be established prior to initiation of Gavreto therapy.

Dosage

Adults

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

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

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

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

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

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

Table 1. Recommended Dose Reductions for Gavreto for Adverse Reactions

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

Table 2. Recommended Dose Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
Pneumonitis/Interstitial Lung Disease (ILD)	Grade 1 or 2	Withhold Gavreto until resolution. Resume at a reduced dose as shown in Table 1. Permanently discontinue Gavreto for recurrent ILD/pneumonitis.
	Grade 3 or 4	Discontinue Gavreto.
Hypertension	Grade 3	Withhold Gavreto for Grade 3 hypertension that persists despite optimal antihypertensive therapy. Resume at a reduced dose as shown in Table 1 when hypertension is controlled.
	Grade 4	Discontinue Gavreto.
Hepatic Transaminase Elevations	Grade 3 or 4	Withhold Gavreto and monitor AST/ALT once weekly until resolution to Grade 1 or baseline. Resume at a reduced dose as shown in Table 1. For recurrent events at Grade 3 or higher, discontinue Gavreto.
Hemorrhagic Events	Grade 3 or 4	Withhold Gavreto until resolution to Grade 1. Resume at a reduced dose as shown in Table 1. Discontinue Gavreto for life-threatening or recurrent severe hemorrhagic events.
QT prolongation	Grade 3	Withhold 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 Adverse Reactions	Grade 3 or 4	Withhold Gavreto until improvement to ≤ Grade 2.

		Resume at a reduced dose as shown in Table 1. Permanently discontinue for recurrent Grade 4 adverse reactions.

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

Dose modifications for specific medicine interactions

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

Avoid coadministration of Gavreto with known strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inhibitors (see section *4.5 Interactions with Other Medicines*). If coadministration with a strong CYP3A4 inhibitor or combined P-gp and strong CYP3A4 inhibitor cannot be avoided, reduce the current dose of Gavreto as recommended in Table 3. After the strong CYP3A4 inhibitor or combined P-gp and strong CYP3A4 inhibitor has been discontinued for 3 to 5 elimination half-lives, the Gavreto dose that was taken prior to the inhibitor can be resumed.

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

Current Gavreto Dosage	**Recommended Gavreto Dosage**
400 mg orally once daily	200 mg orally once daily
300 mg orally once daily	200 mg orally once daily
200 mg orally once daily	100 mg orally once daily

Dose Modification for Use with Strong CYP3A4 Inducers

Avoid coadministration of pralsetinib with strong CYP3A4 inducers (see section *4.5 Interactions with Other Medicines*). If coadministration with a strong CYP3A4 inducer cannot be avoided, the dose of pralsetinib should be increased to double the current pralsetinib dose starting on Day 7 of coadministration of pralsetinib with the strong CYP3A4 inducer. After the strong CYP3A4 inducer has been discontinued for at least 14 days, the Gavreto dose that was taken prior to the use of the strong CYP3A4 inducer can be resumed.

Special populations

Paediatric Populations

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

Elderly Patients
No dose adjustment of Gavreto is required in patients ≥ 65 years of age (see section 5.2 *Pharmacokinetic properties*)

Renal Impairment
No dose adjustment is required in patients with mild or moderate renal impairment. The safety and efficacy of Gavreto have not been studied in patients with severe renal impairment (see section 5.2 *Pharmacokinetic properties*). Since pralsetinib elimination via the kidney is negligible, no dose adjustment is required in patients with severe renal impairment or end-stage renal disease.

Hepatic Impairment
No dose adjustment is required for patients with mild hepatic impairment. The safety and efficacy of Gavreto have not been studied in patients with moderate or severe hepatic impairment, therefore its use in patients with moderate or severe hepatic impairment is not recommended (see section 5.2 *Pharmacokinetic properties*).

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Pneumonitis/Interstitial Lung Disease
Cases of severe, life-threatening, and fatal pneumonitis/interstitial lung disease (ILD) have been reported in clinical trials with Gavreto. Patients should be monitored for acute or worsening of pulmonary symptoms indicative of pneumonitis/ILD (e.g., dyspnoea, cough, and fever). Based on the severity of confirmed pneumonitis/ILD, Gavreto should be withheld, dose reduced, or permanently discontinued (see section 4.2 *Dose and method of administration*).

Hypertension
Hypertension has been reported in clinical trials with Gavreto. Do not initiate Gavreto in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Gavreto. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. In case of severe and persistent hypertension, Gavreto should be withheld, dose reduced, or permanently discontinued (see section 4.2 *Dose and method of administration*).

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

Haemorrhagic events
Severe, including fatal, haemorrhagic events can occur with Gavreto. In patients with life-threatening or recurrent severe bleeding, Gavreto should be permanently discontinued (see section 4.2 *Dose and method of administration*).

QT prolongation
Prolongation of the QT interval has been observed in patients who received Gavreto in clinical trials (see section 4.8 *Adverse effects (undesirable effects)*). 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).

Gavreto 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 *Dose and method of administration*).

Tumour Lysis Syndrome
Cases of tumour lysis syndrome (TLS) have been reported in patients with medullary thyroid carcinoma receiving Gavreto (see section 4.8 *Adverse effects (undesirable effects))* Patients may be at risk of TLS if they have rapidly growing tumours, a high tumour burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

Risk of Impaired Wound Healing
Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, Gavreto has the potential to adversely affect wound healing.
Withhold Gavreto for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Gavreto after resolution of wound healing complications has not been established.

Embryo-Fetal Toxicity
Based on findings from animal studies and its mechanism of action, Gavreto has the potential to cause fetal harm when administered to pregnant women (see section 4.6 *Fertility, pregnancy and lactation*). There are no available data on the use of Gavreto in pregnant women. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryolethality at maternal exposures below the human exposure at the recommended clinical dose of 400 mg once daily (see section 4.6 *Fertility, pregnancy and lactation*).

Women of childbearing potential should be advised of the potential risk to a fetus, and to avoid becoming pregnant whilst receiving Gavreto. Female patients of reproductive potential must use effective non-hormonal contraception during treatment with Gavreto because Gavreto 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.

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

Paediatric use
Safety and efficacy in paediatric patients below the age of 18 years have not been established.

Use in hepatic impairment
Gavreto has not been studied in patients with moderate (total bilirubin > 1.5 to 3 times ULN) or severe (total bilirubin > 3 times ULN) hepatic impairment therefore its use in patients with moderate or severe hepatic impairment is not recommended (see sections 4.2 *Dose and method of administration* and 5.2 *Pharmacokinetic properties*).

Use in renal impairment
Gavreto has not been studied in patients with severe (CLcr < 30 mL/min) renal impairment (see sections 4.2 *Dose and method of administration* and 5.2 *Pharmacokinetic properties*).

Use in the elderly
In the ARROW study (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.

Effects on laboratory tests
See section 4.8 *Adverse effects (undesirable effects) – Laboratory abnormalities.*

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In vitro data indicate that pralsetinib is primarily metabolised by CYP3A4 and to a lesser extent, by CYP2D6 and CYP1A2, and UGT1A4. Pralsetinib is also transported by P-gp. Therefore, inducers and/or inhibitors of CYP3A4 and P-gp may alter the plasma concentrations of pralsetinib.

Effects of Other Drugs on Pralsetinib

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

Avoid coadministration of Gavreto with strong CYP3A4 inhibitors or with combined P-gp and strong CYP3A4 inhibitors. If coadministration with a combined P-gp and strong CYP3A4 inhibitor cannot be avoided, reduce the Gavreto dose (see section 4.2 *Dose and method of administration*). Coadministration of Gavreto with a strong CYP3A4 inhibitor or combined P-gp and strong CYP3A4 inhibitors may increase pralsetinib plasma concentrations and may result in increased adverse reactions.

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

Avoid coadministration of Gavreto with strong CYP3A4 inducers. If coadministration cannot be avoided, increase the Gavreto dose (see section 4.2 *Dose and method of administration*). Coadministration of Gavreto with a strong CYP3A4 inducer may decrease pralsetinib plasma concentrations and may result in decreased efficacy of pralsetinib.

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

Sensitive substrates of CYP3A4, CYP2C8, CYP2C9, P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1 and MATE2K 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

Effects on Fertility
In a dedicated fertility and early embryonic development study conducted in treated male rats mated to treated female rats, pralsetinib did not have clear effects on male or female mating performance or ability to become pregnant. In a 13-week repeat-dose toxicology study however, male rats exhibited histopathological evidence of tubular degeneration/atrophy in the testis with secondary cellular debris and reduced sperm in the lumen of the epididymis, which correlated with lower mean testis and epididymis weights and gross observations of soft and small testis. Female rats exhibited degeneration of the corpus luteum in the ovary. For both sexes, these effects were observed at pralsetinib doses ≥10 mg/kg/day, approximately 1-fold the human exposure based on AUC at the clinical dose of 400 mg.

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

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. Men and women should seek advice on effective fertility preservation before treatment

Use in pregnancy - Category D
There are no available data on the use of Gavreto in pregnant women. Based on findings from animal studies and its mechanism of action, Gavreto has the potential to cause fetal harm when administered to pregnant women. In an embryo-fetal development study, once daily oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in 100% post-implantation loss at dose levels ≥20 mg/kg (approximately 1.8 times the human exposure based on area under the curve [AUC] at the clinical dose of 400 mg). Post-implantation loss also occurred at the 10 mg/kg dose level (approximately 0.6 times the human exposure based on AUC at the clinical dose of 400 mg). Once daily oral administration of pralsetinib at dose levels ≥5 mg/kg (approximately 0.2 times the human AUC at the clinical dose of 400 mg) resulted in an increase in visceral malformations and variations (absent or small kidney and ureter, absent uterine horn, malpositioned kidney or

testis, retroesophageal aortic arch) and skeletal malformations and variations (vertebral and rib anomalies and reduced ossification).

Female patients of reproductive potential must be advised to avoid pregnancy while receiving Gavreto (see section 4.4 *Special warnings and precautions for use*). Patients receiving Gavreto should be advised of the potential hazard to the fetus. Gavreto should not be used during pregnancy Test for pregnancy in females of reproductive potential prior to initiating Gavreto. Female patients should be advised to contact their doctor, should pregnancy occur or if pregnancy is suspected, while taking Gavreto.

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

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

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (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-positive thyroid cancer), who received pralsetinib at a starting dose of 400 mg. 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 4), 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 4. 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			

System organ class / Adverse reactions	Frequency category	All grades %	Grades 3-4 %
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[*]	Very common	46.0	5.7
Alanine aminotransferase increased[*]		33.9	4.2
Hyperbilirubinaemia[15]		13.4	1.3
Skin and subcutaneous tissue disorders			
Rash[16]	Very common	17.2	-
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[17]	Very common	39.8	2.1
Blood creatine phosphokinase increased		16.3	6.4
General disorders and administration site conditions			
Fatigue[18]	Very common	37.3	4.0
Oedema[19]		28.2	0.2
Pyrexia		25.2	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 *Special warnings and precautions for use*). 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 the ARROW study (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 registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agent, 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 the highest selectivity for RET.

RET fusion proteins and activating point mutations can drive tumorigenic potential through hyperactivation of downstream signalling pathways leading to uncontrolled cell proliferation. Pralsetinib exhibited anti-tumour activity in cultured cells and animal tumour implantation models representing multiple tumour types harbouring 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).

Clinical trials

RET Fusion-Positive Non-Small Cell Lung Cancer
The efficacy of Gavreto was evaluated in patients with RET fusion-positive metastatic NSCLC in a multicenter, non-randomized, open-label, multi-cohort clinical trial (ARROW). The study enrolled, in separate cohorts, patients with metastatic RET fusion-positive NSCLC who had progressed on platinum-based chemotherapy and treatment-naïve patients with metastatic NSCLC. Identification of a RET gene fusion was determined by local laboratories using next generation sequencing (NGS), fluorescence in situ hybridization (FISH), and other tests. Among the 114 patients in the efficacy population(s) described in this section, samples from 59% of patients were retrospectively tested with the Life Technologies

Corporation Oncomine Dx Target Test (ODxTT). Patients with asymptomatic central nervous system (CNS) metastases, including patients with stable or decreasing steroid use within 2 weeks prior to study entry, were enrolled. Patients received Gavreto 400mg orally once daily until disease progression or unacceptable toxicity.

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

Metastatic RET Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy
Efficacy was evaluated in 87 patients with RET fusion-positive NSCLC with measurable disease who were previously treated with platinum chemotherapy enrolled into a cohort of ARROW.

The median age was 60 years (range: 28 to 85); 49% were female, 53% were White, 35% were Asian, 6% were Hispanic/Latino. ECOG performance status was 0-1 (94%) or 2 (6%), 99% of patients had metastatic disease, and 43% had either a history of or current CNS metastasis.

Patients received a median of 2 prior systemic therapies (range 1–6); 45% had prior anti-PD-1/PD-L1 therapy and 25% had prior kinase inhibitors. A total of 52% of the patients received prior radiation therapy. RET fusions were detected in 77% of patients using NGS (45% tumour samples; 26% blood or plasma samples, 6% unknown), 21% using FISH, and 2% using other methods. The most common RET fusion partners were KIF5B (75%) and CCDC6 (17%). Efficacy results for RET fusion-positive NSCLC patients who received prior platinum-based chemotherapy are summarized in Table 5.

Table 5. Efficacy Results in ARROW (Metastatic RET Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy)

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

NE = not estimable
a Confirmed overall response rate assessed by BICR
b Calculated using the proportion of responders with an observed duration of response at least 6 months or greater

For the 39 patients who received an anti-PD-1 or anti-PD-L1 therapy, either sequentially or

concurrently with platinum-based chemotherapy, an exploratory subgroup analysis of ORR was 59% (95% CI: 42, 74) and the median DOR was not reached (95% CI: 11.3, NE).

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

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

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

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

Table 6. Efficacy Results for ARROW (Treatment-Naïve Metastatic RET Fusion-Positive NSCLC

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

NE = not estimable
a Confirmed overall response rate assessed by BICR

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)

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). 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 tumour 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 7.

Table 7. 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 Calculated using the proportion of responders with an observed duration of response at least 6 months or greater

5.2 PHARMACOKINETIC PROPERTIES

Following administration of pralsetinib once daily, steady state was reached by 3-5 days. After single dose and repeat dosing of pralsetinib once daily, a dose-dependent increase in systemic exposure was observed over the dose range of 60-600 mg; however, the increase was not dose proportional. At 400 mg QD dosing, the steady-state mean accumulation ratio (%CV) based on AUC was 2.46 (1.83%). The steady state geometric mean [% coefficient of variation (CV %)] of maximum observed plasma concentration (Cmax) and area under the concentration-time curve (AUC0-24h) of pralsetinib at 400 mg was 2470 (55.1%) ng/mL and 36700 (66.3%) h•ng/mL, respectively.

Absorption

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

Effect of food

Food had an effect on both the rate and extent of absorption. Pralsetinib C_{max} and $AUC_{0\text{-}inf}$ were increased by 104% and 122%, respectively in healthy subjects who were administered

pralsetinib after a standardized high-fat meal (~800-1000 calories and ~50 – 60% of calories from fat) compared to the C_{max} and $AUC_{0\text{-}inf}$ after overnight fasting.

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

Gavreto is recommended to be administered on an empty stomach.

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

Metabolism
In vitro studies demonstrated that the oxidative metabolism of pralsetinib is primarily mediated by CYP3A4 with minor contribution from CYP2D6 and CYP1A2; while glucuronidation is primarily catalyzed by UGT1A4. Following a single oral dose of approximately 310 mg of radiolabeled pralsetinib to healthy subjects, pralsetinib metabolites from oxidation (M531, M453, M549b) and glucuronidation (M709) were detected as 5% or less.

Excretion
The mean (±standard deviation) plasma elimination half-life of pralsetinib was 15.7 hours (9.8) following single doses and 20 (11.7) hours following multiple doses of pralsetinib. Following oral administration of pralsetinib 400 mg once daily, the steady state geometric mean apparent oral clearance (CL/F) was 10.9 L/h (66%).

Following a single oral dose of ~ 310 mg administered as 3 x 100 mg capsules plus one capsule containing ~10 mg (~100 μCi) [14C]pralsetinib to healthy subjects, 73% of the radioactive dose was recovered in faeces and 6% was recovered in urine. Unchanged pralsetinib represented approximately 66% and 4.8% of the total radioactive dose in faeces and urine, respectively.

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

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

Hepatic impairment
As hepatic elimination is a major route of excretion for Gavreto, hepatic impairment may result in increased plasma concentrations. Based on a population pharmacokinetic analysis, Gavreto exposures were similar between 7 subjects with mild hepatic impairment (total

bilirubin within upper limit of normal [ULN] and AST > ULN or total bilirubin >1 to 1.5 times ULN and any AST) and 175 subjects with normal hepatic function (total bilirubin and AST within ULN). The pharmacokinetics of Gavreto in patients with moderate (total bilirubin >1.5 to 3.0 × upper limit of normal [ULN] and any aspartate aminotransferase [AST]) or severe hepatic impairment (total bilirubin >3.0 times ULN and any AST) have not been studied.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

Carcinogenicity studies with pralsetinib have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule content

Hypromellose
Microcrystalline cellulose
Sodium bicarbonate
Citric acid, anhydrous
Magnesium stearate
Pregelatinized Starch

Capsule shell

Hypromellose
Titanium dioxide
Brilliant blue FCF

Printing ink

TekPrint™ SW-0012 White Ink (PI no. 13175)

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Keep the bottle tightly closed to protect from moisture.

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

6.5 NATURE AND CONTENTS OF CONTAINER

Gavreto 100 mg capsules are contained in an HDPE bottle, and are supplied as follows:

- Bottles of 60 capsules (AUST R 380812)
- Bottles of 90 capsules (AUST R 380812)
- Bottles of 120 capsules (AUST R 380812)

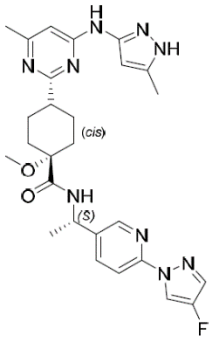
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure



CAS number

2097132-94-8

The chemical name for pralsetinib is (cis)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-(5- methyl-1H-pyrazol-3-ylamino)pyrimidin-2-l)cyclohexanecarboxamide. The molecular formula for pralsetinib is $C_{27}H_{32}FN_9O_2$, and the molecular weight is 533.61 g/mol. The solubility of pralsetinib in aqueous media decreases over the range pH 1.99 to pH 7.64 from
0.880 mg/mL to <0.001 mg/mL, indicating a decrease in solubility with increasing pH.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

29 March 2023

10. DATE OF REVISION

6 April 2023

Summary table of changes

Section Changed	Summary of new information
4.1, 4.2, 4.4, 4.8, 5.1	New Indication (RET-fusion positive Thyroid cancer)