Date: 22 September 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Gavreto

International non-proprietary name: pralsetinib

Pharmaceutical form: hard capsules

Dosage strength: 100 mg

Route(s) of administration: oral

Marketing Authorisation Holder: Roche Pharma (Schweiz) AG

Marketing Authorisation No.: 68182

Decision and Decision date: approved (temporary authorisation in accordance with Art. 9a TPA) on 12 August, 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Table of contents

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DTC	differentiated thyroid carcinoma
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MTC	medullary thyroid cancer
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
NSCLC	Non-small cell lung cancer
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
PTC	papillary thyroid carcinoma
RET	REarranged during Transfection
RMP	Risk Management Plan
RTK	receptor tyrosine kinase
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance pralsetinib of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA. The Orphan Status was granted on 3 November 2020.

Authorisation human medical product under Art. 13 TPA
The applicant requested a reduced assessment procedure in accordance with Art. 13 TPA.

Temporary authorisation for human medical products
The applicant requested a temporary authorisation in accordance with Art. 9a TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

GAVRETO is indicated for the treatment of adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) and who have experienced progression after previous treatment.

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

GAVRETO is indicated for the treatment of adult and paediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who have experienced progression after previous treatment including radioactive iodine.

The presence of a RET gene fusion (NSCLC or thyroid cancer) or RET gene mutation (MTC) must be confirmed by a validated test for RET fusions and RET mutations before starting therapy with Gavreto.

2.2.2 Approved Indication

RET Fusion-Positive Non-Small Cell Lung Cancer
Gavreto is indicated for the treatment of adult patients with metastatic RET fusion-positive (RET = REarranged during Transfection) non-small cell lung cancer (NSCLC) who require systemic therapy and who have experienced progression after prior treatment (see "Clinical efficacy").

RET-Mutant Medullary Thyroid Cancer
Gavreto is indicated for the treatment of adult patients with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy and who have experienced progression after prior treatment with tyrosine kinase inhibitors (see "Clinical efficacy").

RET Fusion-Positive Thyroid Cancer
Gavreto is indicated for the treatment of adult patients with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who have experienced progression after prior treatment including radioactive iodine (see "Clinical efficacy").

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

The efficacy and safety of Gavreto was not studied in patients with other oncogene driver mutations (see “Warnings and precautions”).

2.2.3 Requested Dosage

The recommended dosage of GAVRETO is 400 mg orally once daily on an empty stomach (no food intake for at least 2 hours before and at least 1 hour after taking GAVRETO).
Continue treatment until disease progression or until unacceptable toxicity.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	12 April 2021
Formal control completed	22 April 2021
Predecision	10 June 2021
Answers to Predecision	11 July 2021
Final Decision	12 August 2021
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

Swissmedic has not assessed all the primary data of this application and relies for its decision on the assessment of the foreign reference authority, the US-FDA. The current SwissPAR refers to the publicly available Assessment Report Gavreto (Application number NDA 213721; approval date: 4 September 2020) issued by the US-FDA.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

3 Medical Context

RET is a receptor tyrosine kinase (RTK) and contributes to the maintenance of neural, neuroendocrine, haematopoietic and male germ cell tissues. Aberrantly activated RET can act as an oncogene in multiple malignancies.
RET rearrangements involve the 3'sequence of RET and the 5'sequence other partner genes. Clinical data suggest that these rearrangements occur in up to 10%-20% of papillary thyroid cancer, 2% of NSCLC and in other solid tumours (colon < 1%, pancreatic cancer < 1% and spitzoid melanoma < 1%).[1]

1. RET fusion-positive Non-Small Cell Lung Cancer (NSCLC):
   NSCLC accounts for 80% of lung cancers, and adenocarcinoma is the most common histological subtype. The anticipated 5-year survival for patients with clinical stage IIIB NSCLC is approximately 26% and less than 5% for patients who present with clinical stage IV disease[1]. RET gene fusions have been identified in 1-2% of NSCLC, in particular adenocarcinoma predominantly with KIF5B 83.6% and CCDC6 15.1% RET fusions.[6] Patients with NSCLC and RET rearrangements have the following clinico-pathological characteristics: age ≤ 60 years, poorly differentiated tumours and no prior history of smoking. Patients with RET-driven NSCLC are currently treated with the standard of care for second-line NSCLC (chemotherapies, immune checkpoint inhibitors) regardless of RET mutation.

2. RET-mutant Medullary Thyroid Cancer (MTC)
   MTC is a rare thyroid tumour accounting for approximately 3%-5% of all thyroid cancers. Most cases are already at an advanced stage at diagnosis. The prognosis is unfavourable, with a 5-year survival rate of approximately 86% and a 10-year survival rate of 50-65%.[2]
   Activating mutations in the RET gene are the main driver mutations in medullary thyroid cancer. Approximately 50% of sporadic forms carry a somatic RET mutation, and familial cases have an identifiable germline mutation in at least 90% of cases.[3]
   As initial treatment, complete surgical resection is recommended. In cases of aggressive local disease, external beam radiotherapy is possible. Systemic therapy should be initiated if metastatic lesions and disease progression are present after initial therapy.
   For patients with MTC and distant metastases who are symptomatic or have progressive disease, vandetanib and cabozantinib are treatments of choice. However, these treatments are associated with relevant toxicity, which represents a major limitation of these therapies. In particular, adverse events (AE) such as QT prolongation, fatigue, or weight loss require dose reductions and can severely affect the quality of life of these patients.[3]

3. RET fusion-positive thyroid cancer
   Papillary thyroid carcinoma (PTC) is the most common (~80%) malignancy of the thyroid gland. RET fusion-positive thyroid cancer consists of two forms: differentiated thyroid carcinoma (DTC) and poorly differentiated thyroid cancer. Differentiated thyroid carcinoma (DTC) includes the histologic subtypes of papillary, follicular and Hurthle cell carcinoma and can occur in the paediatric population. DTC accounts for 1.4% of all paediatric malignancies, and the most common form is papillary thyroid carcinoma.[4]
   Approximately 5 – 20% of papillary thyroid carcinomas have RET rearrangements, which are more commonly detected in children than in adults, possibly because of the high proliferation rate of thyroid follicular cells in children.[5,6] RET fusions are uncommon in thyroid cancer subtypes other than PTC. In particular, the second common type, follicular thyroid carcinoma, is generally negative for RET fusion.[7] In addition, the prevalence is much higher in radiation-induced papillary thyroid cancer.[3] RET fusions are more common in radiation-associated than in "sporadic" cases. The most common RET rearrangements are CCDC6 59% and NCOA4 36%.[6]
   Standard of care in patients with DTC is thyroidectomy or lobectomy, as well as postoperative treatment with radioactive iodine (RAI) therapy for patients at high risk of persistent disease or

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

disease recurrence after total thyroidectomy. This therapy is curative in most cases. However, 30% of patients have recurrence of disease. Relevant prognostic factors are age, incomplete resection, metastases and tumour size. For patients with radioactive iodine-refractory differentiated thyroid cancer (RR-DTC), treatment options are limited. Two tyrosine kinase inhibitors (TKIs) are authorised in Switzerland for RR-DTC: sorafenib and lenvatinib. However, these therapies are associated with significant risks, such as hypertension and hand-foot syndrome.

[1] Rami-Porta et al. Lung Cancer - Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual. CA Cancer J Clin. 2017 Mar;67(2):138-155.
[2] Viola et al. Management of Medullary Thyroid Cancer. Endocrinol Metab Clin N Am 48 (2019) 285–301
[3] Thomas et al. Diagnosis and pathologic characteristics of medullary thyroid carcinoma—review of current guidelines. Current Oncology, Vol. 26, No. 5, October 2019
[4] Verburg et al. Radioactive Iodine (RAI) Therapy for Metastatic Differentiated Thyroid Cancer. Best Pract Res Clin Endocrinol Metab. 2017 Jun;31(3):279-290.
[5] A Drilo. TRK Inhibitors in TRK Fusion-Positive Cancers. Ann Oncol. 2019 Nov;30 Suppl 8:viii23-viii30
[6] Subbiah et al. State-of-the-Art Strategies of Targeting RET-Dependent Cancers. J Clin Oncol 38:1209-1221
[7] Santoro et al. RET Gene Fusions in Malignancies of the Thyroid and Other Tissues. Genes (Basel). 2020 Apr 15;11(4):424.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

4 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and relies for its decision on the assessment of the foreign reference authority, the US-FDA. The current SwissPAR relating to quality aspects refers to the publicly available Assessment Report Gavreto (Application number NDA 213721; approval date: 4 September 2020 issued by the US-FDA.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

5 Nonclinical Aspects

Swissmedic has not assessed the primary data relating to preclinical aspects of this application and relies for its decision on the assessment of the foreign reference authority, the US-FDA. The current SwissPAR relating to preclinical aspects refers to the publicly available Assessment Report Gavreto (Application number NDA 213721; approval date: 4 September 2020) issued by the US-FDA.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

Swissmedic has not assessed the primary data relating to clinical pharmacology aspects of this application and its decision relies on the results of the assessment of the foreign reference authority, the FDA. The current SwissPAR relating to clinical pharmacology aspects refers to the publicly available Assessment Report GAVRETO™ (Application number NDA 213721; approval date: 4 September 2020) issued by the US-FDA.

6.2 Dose Finding and Dose Recommendation and Efficacy

This application was submitted according to article 13, and the evaluation is partly based on the assessment of the foreign reference authority, the FDA. The current SwissPAR relating to clinical aspects refers to the publicly available FDA Assessment Report for GAVRETO. Swissmedic focused the evaluation on the submitted second-line indications (see below), which differ from the indication accepted by the FDA.

The applicant submitted one pivotal study, BLU-667-1101, for evaluation of efficacy and safety.

Efficacy of pralsetinib in RET fusion-positive NSCLC with progression after platinum chemotherapy
Patients previously treated with platinum chemotherapy demonstrate a durable Overall Response Rate (ORR 57%) with pralsetinib that is superior to the ORR demonstrated with standard second-line therapies and comparable to other approved RET targeted therapies in Switzerland.

Efficacy of pralsetinib in RET-mutant MTC with progression after tyrosine kinase inhibitors
The ORR (60%) of pralsetinib in the adult population is compelling compared to historical results for approved tyrosine kinase inhibitors.

Efficacy of pralsetinib in RET-fusion thyroid cancer with progression after previous therapy including radioactive iodine (RAI) therapy
The ORR (89%) of pralsetinib in the adult population is compelling compared to historical results, in particular for papillary carcinoma.

Other oncogenic driver mutations
Study BLU-667-1101 excluded patients with other oncogenic driver mutations. In particular, patients with NSCLC and EGFR, ALK, ROS1 and BRAF mutations were excluded per protocol. This aspect is reflected in the indication.

Paediatric population (all indications)
No data are available for paediatric patients (NSCLC: median age 60 years, range 28-85 years, MTC: median age 59 years, range 25-83 years, Thyroid: median age 61, range 46-74 years).

6.3 Safety

Pralsetinib is associated with severe toxicities. Relevant risks such as pneumonitis, hepatotoxicity, haemorrhagic events, hypertension, delayed wound healing, tumour lysis syndrome and increased creatine phosphokinase are addressed in the product information (see attached product information). Overall, the toxicity profile of pralsetinib is considered acceptable and manageable taking account of the fact that treatment will be initiated by a specialist in oncology.

6.4 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Limited therapies are approved specifically for patients with RET-driven cancers such as RET fusion-positive NSCLC, RET fusion-positive thyroid cancer or RET-mutant MTC. Patients with RET-driven cancers are currently treated with the standard of care for patients with their tumour type, regardless of the RET alteration. In 2021, the first RET targeted therapy was approved in Switzerland for RET altered cancers.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

ORR results are compelling for RET fusion-positive NSCLC, RET-mutant MTC and RET fusion-positive thyroid cancer in second-line treatment, and can be accepted for a temporary authorisation. However, updated results of the pivotal study BLU-667-1101 and, in addition, results of randomised phase III trials are necessary for confirmation. The applicant will submit results of the studies AcceleRET-MTC/CO42865 and integrated analyses of the studies RET ARROW ((BLU-667-1101/BO42863) and TAPISTRY (BO41932) as a requirement for accepted temporary authorisation.

6.5 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Gavreto was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Gavreto has received temporary authorisation, see section “Properties/Effects”.

Gavreto®

Composition

Active substances

Pralsetinibum.

Excipients

Hypromellosum, cellulosum microcristallinum, natrii hydrogenocarbonas, acidum citricum anhydricum, magnesii stearas, amylum pregelificatum. 1 hard capsule contains 22.3 mg sodium.
Capsule shell:
Hypromellosum, titanii dioxidum, ceruleum nitens FCF (E133).
Ink:
Lacca, propylenglycolum, ammonii hydroxidi solutio concentrata, Kalii hydroxydum, titanii dioxidum.

Pharmaceutical form and active substance quantity per unit

Gavreto (pralsetinib) is supplied for oral use.
Hard capsule: Each hard capsule contains 100 mg pralsetinib. Light blue, opaque Hypromellosum hard capsule printed with “BLU-667” on the capsule shell (“body”) and “100 mg” on the capsule shell cap.

Indications/Uses

RET Fusion-Positive Non-Small Cell Lung Cancer
Gavreto is indicated for the treatment of adult patients with metastatic RET fusion-positive (RET = REarranged during Transfection) non-small cell lung cancer (NSCLC) who require systemic therapy and who have experienced progression after prior treatment (see “Clinical efficacy”).
RET-Mutant Medullary Thyroid Cancer
Gavreto is indicated for the treatment of adult patients with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy and who have experienced progression after prior treatment with tyrosine kinase inhibitors (see “Clinical efficacy”).
RET Fusion-Positive Thyroid Cancer

Gavreto is indicated for the treatment of adult patients with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who have experienced progression after prior treatment including radioactive iodine (see “Clinical efficacy”).
The efficacy and safety of Gavreto was not studied in patients with other oncogene driver mutations (see “Warnings and precautions”).”

Dosage/Administration

General

Patient Selection

The presence of a RET-gene fusion (NSCLC and non-medullary thyroid cancer) or a mutation (MTC) has to be confirmed prior to a therapy with Gavreto with a validated test for RET-fusions and RET-mutations.

Usual dosage

The recommended dosage of Gavreto is 400 mg orally once daily on an empty stomach (no food intake for at least 2 hours before and at least 1 hour after taking Gavreto) (see “Pharmacokinetics”).

Duration of treatment

Patients should be treated until disease progression or until occurrence of unacceptable toxicity with Gavreto.

Dose adjustment following undesirable effects/interactions

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

Tabelle 1: Recommended Dose Reductions for Gavreto for Adverse Reactions

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

Permanently discontinue Gavreto in patients who are unable to tolerate 100 mg taken orally once daily.
The recommended dosage modifications for adverse reactions are provided in Table 2.

Tabelle 2: Recommended Dosage Modifications for Gavreto for Adverse Reactions (see «Warnings and precautions»)

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

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

Combination therapy

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

Avoid coadministration of Gavreto with known combined P-gp and strong CYP3A inhibitors. If coadministration with a combined P-gp and strong CYP3A inhibitor cannot be avoided, reduce the current dose of Gavreto as recommended in Table 3. After the inhibitor has been discontinued for 3 to

5 elimination half-lives, resume Gavreto at the dose taken prior to initiating the combined P-gp and strong CYP3A inhibitor (see “Interactions” and “Pharmacokinetics”).

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

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

Dose Modification for Use with Strong CYP3A Inducers

Avoid coadministration of Gavreto with strong CYP3A inducers. If coadministration with a strong CYP3A inducer cannot be avoided, increase the starting dose of Gavreto to double the current Gavreto dosage starting on Day 7 of coadministration of Gavreto with the strong CYP3A inducer. After the inducer has been discontinued for at least 14 days, resume Gavreto at the dose taken prior to initiating the strong CYP3A inducer (see “Interactions” and “Pharmacokinetics”).

Patients with hepatic disorders

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

Elderly patients

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

Children and adolescents

The safety and efficacy of pralsetinib in paediatric patients below 18 years of age have not been established. No data are available.

Delayed administration

If a dose of Gavreto is missed, it can be taken as soon as possible on the same day. Resume the regular daily dose schedule for Gavreto the next day.
Do not take an additional dose if vomiting occurs after Gavreto but continue with the next dose as scheduled.

Contraindications

Hypersensitivity to the active substance or any of the excipients listed under “Composition”.

Warnings and precautions

Interstitial Lung Disease/Pneumonitis

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

Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold Gavreto and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue Gavreto based on severity of confirmed ILD (see “Dosage/Administration”).

Hypertension

Hypertension occurred in 29% of patients, including Grade 3 hypertension in 14% of patients (see “Undesirable effects”). Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications.

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

Hepatotoxicity

Serious hepatic adverse reactions occurred in 2.1% of patients treated for Gavreto. Increased AST occurred in 69% of patients, including Grade 3 or 4 in 5% and increased ALT occurred in 46% of patients, including Grade 3 or 4 in 6% (see “Undesirable effects”). The median time to first onset for increased AST was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 1.7 years).

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

Hemorrhagic Events

Serious, including fatal, hemorrhagic events can occur with Gavreto. Grade ≥ 3 hemorrhagic events occurred in 2.5% of patients treated with Gavreto including one patient with a fatal hemorrhagic event. Permanently discontinue Gavreto in patients with severe or life-threatening hemorrhage (see “Dosage/Administration”).

QT prolongation

Prolongation of the QT interval has been observed in patients who received Gavreto in clinical trials (see “Undesirable effects”). Therefore, before starting Gavreto treatment, patients should have a QTc interval ≤470 ms, serum electrolytes and TSH 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. Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Monitor the QT interval more frequently when pralsetinib is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Pralsetinib has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction.

Gavreto may require interruption, dose modification, or discontinuation (see “Dosage/Administration”).

Tumor Lysis Syndrome

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

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 can cause fetal harm when administered to a pregnant woman. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryolethality at maternal exposures below the human exposure at the clinical dose of 400 mg once daily. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with Gavreto and for 2 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Gavreto

and for 1 week after the final dose (see sections “Dosage/Administration: Special dosage instructions”, “Pregnancy, lactation” and “Preclinical data”).

Growth plate abnormalities

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

Concomitant oncogenic driver alterations

The efficacy and safety of Gavreto in patients with concomitant oncogenic driver alterations has not been established. The following targetable, treatable driver alterations have been excluded from BLU-667-1101 study:

- NSCLC: with targetable, treatable alterations in EGFR, ALK, ROS1 or BRAF.

Sodium

Gavreto contains up to 22.3 mg sodium per capsule, 89.2 mg per daily dose respectively. This corresponds to 4.46% of the recommended maximal daily sodium uptake with food for an adult.

Interactions

Effect of other agents on the pharmacokinetics of Pralsetinib

Strong CYP3A Inhibitors

Avoid coadministration of Gavreto with strong CYP3A inhibitors. Coadministration of Gavreto with a strong CYP3A inhibitor increases pralsetinib exposure, which may increase the incidence and severity of adverse reactions of Gavreto.

Avoid coadministration of Gavreto with combined P-gp and strong CYP3A inhibitors. If coadministration with a combined P-gp and strong CYP3A inhibitor cannot be avoided, reduce the Gavreto dose (see “Dosage/Administration” and “Pharmacokinetics”). Coadministration of itraconazole 200 mg once daily with a single Gavreto 200 mg dose increased pralsetinib C_{max} by 84% (90% CI: 50%-125%) and $AUC_{0\text{-}INF}$ by 251% (90% CI: 186%-332%).

Strong CYP3A Inducers

Coadministration of Gavreto with a strong CYP3A inducer decreases pralsetinib exposure, which may decrease efficacy of Gavreto. Avoid coadministration of Gavreto with strong CYP3A inducers. If coadministration of Gavreto with strong CYP3A inducers cannot be avoided, increase the Gavreto dose (see “Dosage/Administration” and “Pharmacokinetics”).

Coadministration of Rifampin 600 mg once daily with a single Gavreto 400 mg dose decreased pralsetinib C_{max} by 30% (90% CI: 20%-39%) and $AUC_{0\text{-}INF}$ by 68% (90% CI: 63%-73%).

Mild CYP3A Inducers

No clinically significant differences in the PK of pralsetinib were identified when Gavreto was coadministered with mild CYP3A inducers.

Acid-Reducing Agents

No clinically significant differences in the PK of pralsetinib were observed when Gavreto was coadministered with gastric acid reducing agents.

Effect of Pralsetinib on the pharmacokinetics of other agents

Cytochrome P450 (CYP) Enzymes

Pralsetinib is a time-dependent inhibitor of CYP3A4/5 and an inhibitor of CYP2C8, CYP2C9, and CYP3A4/5, but not an inhibitor of CYP1A2, CYP2B6, CYP2C19 or CYP2D6 at clinically relevant concentrations. Pralsetinib is an inducer of CYP2C8, CYP2C9, and CYP3A4/5, but not an inducer of CYP1A2, CYP2B6, or CYP2C19 at clinically relevant concentrations.

Transporter Systems

Pralsetinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but not a substrate of bile salt efflux pump (BSEP), organic cation transporter [OCT]1, OCT2, organic anion transporting polypeptide [OATP]1B1, OATP1B3, multidrug and toxin extrusion [MATE]1, MATE2-K, organic anion transporter [OAT]1, or OAT3. Pralsetinib is an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1, MATE2-K, and BSEP, but not an inhibitor of OCT1, OCT2, and OAT1A3 at clinically relevant concentrations.

Pregnancy, lactation

Women of childbearing age or their partners and contraception

Gavreto can damage the unborn child when used in a pregnant woman (see “Dosage/Administration: Special dosage instructions”). It is recommended to perform a pregnancy test before starting treatment in women who could become pregnant. Women who can become pregnant should be advised to avoid pregnancy during treatment with Gavreto. Female patients should be instructed to use an effective non-hormonal contraceptive method during treatment with Gavreto and for two weeks after the last dose. Gavreto can impair the action of hormonal contraceptives and make them ineffective. Male patients with female partners of childbearing age should be advised to use a reliable contraceptive method during treatment with Gavreto and for at least one week after the last dose. If a patient or the partner of a male patient under treatment with Gavreto becomes pregnant, she must be informed about the possible risk to the unborn child.

Pregnancy

Due to its mechanism of action, Gavreto can lead to damage to the unborn child when administered to pregnant women. There are no data available on the use of Gavreto in pregnant women. In animal studies, embryo lethality, as well as teratogenic effects in rats occurred (see “Preclinical Data”). The potential risk for humans is not known. During pregnancy the drug should not be used, unless it is clearly necessary.

Lactation

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

Fertility

There are no data available on the effect of pralsetinib on human fertility. Animal studies with pralsetinib indicate that male and female fertility can be impaired (see “Preclinical data”).

Effects on ability to drive and use machines

No corresponding studies have been performed.

Undesirable effects

The safety of Gavreto was evaluated in 471 patients treated with 400 mg QD in an openlabel, single-arm study (“ARROW”). Patients with RET-fusion positive NSCLC, RET-mutant medullary thyroid cancer, and other RET-altered advanced solid tumors were included in the study. Patients received a starting dose of 400 mg once daily until intolerance to therapy or disease progression.
The most common undesirable effects (>20%) observed in patients treated with pralsetinib are anemia, neutropenia, leukopenia, hypertension, cough, constipation, diarrhea, aspartate aminotransferase increased, alanine aminotransferase increased, musculoskeletal pain, blood creatinine increased, fatigue, edema, and pyrexia.
The most common serious adverse drug reactions (ADR) are pneumonia (10.0%), pneumonitis (5.1%), anemia (3.0%) and urinary tract infection (3.0%).
Adverse drug reactions from clinical trials are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (=1/10), common (=1/100 to <1/10), uncommon (=1/1000 to <1/100), rare (=1/10,000 to <1/1000), very rare (<1/10,000).

Infection and Infestations
Very common: Pneumonia[1] (All Grades: 13.8%, Grade 3-4: 7.9%, Grade 5: 1.3%), Urinary tract infection (All Grades: 11.3%, Grade 3-4: 3.0%, Grade 5: 0.2%).
Blood and Lymphatic System Disorders
Very common: Anemia[2] (All Grades: 40.6%, Grade 3-4: 14.9%), Neutropenia[3] (All Grades: 39.9%, Grade 3-4: 18.3%), Leukopenia[4] (All Grades: 31.4%, Grade 3-4: 6.4%), Lymphopenia[5] (All Grades: 18.0%, Grade 3-4: 10.6%), Thrombocytopenia[6] (All Grades: 16.3%, Grade 3-4: 4.2%).
Metabolism and nutrition disorders

Very common: Hyperphosphatemia (All Grades: 18.3%, Grade 3-4: 0.2%), Hypocalcemia (All Grades: 17.0%, Grade 3-4: 2.8%).

Common: Hypophosphatemia, Hypoalbuminemia, Hyponatremia.

Nervous system disorders

Very common: Taste disorder[7] (All Grades: 15.7%), Headache[8] (All Grades: 14.4%, Grade 3-4: 0.4%).

Cardiac disorders

Common: QT prolongation.

Vascular Disorders

Very common: Hypertension[9] (All Grades: 30.8%, Grade 3-4: 15.3%), Hemorrhage[10] (All Grades: 10.0%, Grade 3-4: 0.4%, Grade 5: 0.2%).

Respiratory, thoracic and mediastinal disorders

Very common: Cough[11] (All Grades: 22.7%, Grade 3-4: 0.6%), Dyspnea (All Grades: 15.3%, Grade 3-4: 1.7%, Grade 5: 0.2%), Pneumonitis[12] (All Grades: 10.8%, Grade 3-4: 2.8%, Grade 5: 0.2%).

Gastrointestinal disorders

Very common: Constipation (All Grades: 38.9%, Grade 3-4: 0.6%), Diarrhea (All Grades: 28.9%, Grade 3-4: 3.2%), Dry mouth (All Grades: 14.9%), Nausea (All Grades: 14.2%, Grade 3-4: 0.2%), Abdominal pain[13] (All Grades: 13.6%, Grade 3-4: 1.3%), Vomiting (All Grades: 10.8%, Grade 3-4: 1.1%).

Common: Stomatitis[14].

Hepatobiliary Disorders

Very Common: Aspartate aminotransferase (AST) increased (All Grades: 44.2%, Grade 3-4: 5.3%), Alanine aminotransferase (ALT) increased (All Grades: 31.4%, Grade 3-4: 4.2%), Hyperbilirubinemia[15] (All Grades: 14.0%, Grade 3-4: 0.8%).

Common: Blood alkaline phosphatase increased (All Grades: 9.6%, Grade 3-4: 0.8%).

Skin and subcutaneous tissue disorders

Very common: Rash[16] (All Grades: 16.3%).

Musculoskeletal and Connective Tissue Disorders

Very common: Musculoskeletal pain[17] (All Grades: 37.2%, Grade 3-4: 1.9%), Blood creatine phosphokinase increased (All Grades: 11.9%, Grade 3-4: 4.5%).

Renal and Urinary Disorders

Very common: Blood creatinine increased (All Grades: 21.2%, Grade 3-4: 0.2%).

General Disorders and Administration Site Conditions

Very common: Fatigue[18] (All Grades: 34.0%, Grade 3-4: 4.2%, Grade 5: 0.2%), Edema[19] (All Grades: 24.6%, Grade 3-4: 0.2%), Pyrexia (All Grades: 22.3%, Grade 3-4: 1.1%).

[1] Includes the preferred terms: Pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia cytomegaloviral, Atypical pneumonia, Lung infection, Pneumonia bacterial, Pneumonia haemophilus, Pneumonia influenza, Pneumonia streptococcal

[2] Includes the preferred terms: Anaemia, Red blood cell count decreased, Aplastic anaemia, Haematocrit decreased, Haemoglobin decreased
[3] Includes the preferred terms: Neutropenia, Neutrophil count decreased
[4] Includes the preferred terms: Leukopenia, White blood cell count decreased
[5] Includes the preferred terms: Lymphopenia, Lymphocyte count decreased
[6] Includes the preferred terms: Thrombocytopenia, Platelet count decreased
[7] Includes the preferred terms: Dysgeusia, Ageusia
[8] Includes the preferred terms: Headache, Tension Headache
[9] Includes the preferred terms: Hypertension, Blood pressure increased
[10] Includes the preferred terms: Haemorrhage intracranial, Contusion, Gingival bleeding, Ecchymosis, Epistaxis, Upper gastrointestinal haemorrhage, Haemorrhoidal haemorrhage, Gastrointestinal haemorrhage, Cerebellar haemorrhage, Conjunctival haemorrhage, Vaginal haemorrhage
[11] Includes the preferred terms: Cough, Productive Cough
[12] Includes the preferred terms: Pneumonitis, Interstitial lung disease
[13] Includes the preferred terms: Abdominal pain, Abdominal pain upper
[14] Includes the preferred terms: Stomatitis, Aphthous ulcer
[15] includes the preferred terms: blood bilirubin increased, hyperbilirubinaemia, bilirubin conjugated increased, blood bilirubin unconjugated increased
[16] Includes the preferred terms: Rash, Rash maculo-papular, Dermatitis acneiform, Erythema, Rash generalised, Rash papular, Rash pustular, Rash macular, Rash erythematous
[17] Includes the preferred terms: Myalgia, Arthralgia, Pain in extremity, Neck pain, Musculoskeletal pain, Back pain, Musculoskeletal chest pain, Bone pain, Spinal pain, Musculoskeletal stiffness
[18] Includes the preferred terms: Fatigue, Asthenia
[19] Includes the preferred terms: Oedema, Swelling face, Peripheral swelling, Generalised oedema, Oedema peripheral, Face oedema, Periorbital oedema, Eyelid oedema, Swelling, Localised oedema

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose have been reported with Gavreto in clinical studies.

Properties/Effects

ATC code

L01EX23

Mechanism of action

Pralsetinib is a kinase inhibitor of wild-type RET and oncogenic RET fusions (CCDC6-RET) and mutations (RET V804L, RET V804M and RET M918T) with half maximal inhibitory concentrations (IC50s) less than 0.5 nM. In purified enzyme assays, pralsetinib inhibited DDR1, TRKC, FLT3, JAK1-2, TRKA, VEGFR2, PDGFRB, and FGFR1 at higher concentrations that were still clinically achievable at Cmax. In cellular assays, pralsetinib inhibited RET at approximately 14-, 40-, and 12-fold lower concentrations than VEGFR2, FGFR2, and JAK2, respectively.

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

Pharmacodynamics

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

Cardiac Electrophysiology

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

Clinical efficacy

Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer

The efficacy of Gavreto was evaluated in patients with RET fusion-positive metastatic NSCLC in a multicenter, non-randomized, open-label, multi-cohort clinical trial (ARROW, NCT03037385). The study enrolled, in separate cohorts, patients with metastatic RET fusion positive NSCLC who had progressed on platinum-based chemotherapy and treatment-naïve patients with metastatic NSCLC. Identification of a RET gene fusion was determined by local laboratories using next generation sequencing (NGS), fluorescence in situ hybridization (FISH), and other tests. 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% tumor samples; 26% blood or plasma samples, 6% unknown), 21% using FISH, and 2% using other methods. The most common RET fusion partners were KIF5B (75%) and CCDC6 (17%).

The ORR (confirmed CR or PR; assessed by BICR) for the 87 patients with RET fusion-positive metastatic NSCLC who received prior platinum treatment was 57% (95% CI: 46, 68). The median DOR was not reached (95% CI: 15.2, NE).

RET-Mutant Medullary Thyroid Cancer

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

RET-Mutant MTC Previously Treated with Cabozantinib or Vandetanib

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

The median age was 59 years (range: 25 to 83); 69% were male, 78% were White, 5% were Asian, 5% were Hispanic/Latino. ECOG performance status was 0-1 (95%) or 2 (5%), and 7% had a history of CNS metastases. Patients had received a median of 2 prior therapies (range 1-7). RET mutation status was detected in 73% using NGS (55% tumor sample, 18% plasma), 26% using PCR sequencing, and 2% other. The primary mutations in RET-mutant MTC previously treated with cabozantinib or vandetanib are described in Table 4.

Table 4: Primary Mutations in RET-Mutant MTC in ARROW

RET Mutation Type	**Prior Cabozantinib or Vandetanib (n= 55)**
M918T[1]	37
Cysteine Rich Domain[2]	11
V804M or V804L	2
Other[3]	5

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

The ORR (confirmed overall response rate assessed by BICR) for the 55 patients with RET-Mutant MTC previously treated with cabozantinib or vandetanib was 60% (95% CI: 46; 73). The median DOR was not reached (95% CI: 15.1; NE)

RET Fusion-Positive Thyroid Cancer

The efficacy of Gavreto was evaluated in RET fusion-positive metastatic thyroid cancer patients in a multicenter, open-label, multi-cohort clinical trial (ARROW, NCT03037385). All patients with RET fusion-positive thyroid cancer were required to have disease progression following standard therapy,

measurable disease by RECIST version 1.1, and have RET fusion status as detected by local testing (89% NGS tumor samples and 11% using FISH).
The median age was 61 years (range: 46 to 74); 67% were male, 78% were White, 22% were Asian, 11% were Hispanic/Latino. All patients (100%) had papillary thyroid cancer. ECOG performance status was 0-1 (100%), all patients (100%) had metastatic disease, and 56% had a history of CNS metastases. Patients had received a median of 2 prior therapies (range 1-8). Prior systemic treatments included prior radioactive iodine (100%) and prior sorafenib and/or lenvatinib (56%).

The ORR (confirmed overall response rate assessed by BICR) for the 9 patients with RET fusion-positive thyroid cancer was 89% (95% CI: 52, 100). The median DOR was not reached (95% CI: NE; NE).

Temporary authorisation
The medicinal product Gavreto has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation.

Pharmacokinetics

Absorption

At 400 mg Gavreto once daily under fasting conditions, the steady state geometric mean [% coefficient of variation (CV%)] of maximum observed plasma concentration (C_{max}) and area under the concentration-time curve (AUC_{0-24h}) of pralsetinib was 2470 (55.1%) ng/mL and 36700 (66.3%) h•ng/mL, respectively. Pralsetinib C_{max} and AUC increased inconsistently over the dose range of 60 mg to 600 mg once daily (0.15 to 1.5 times the recommended dose). Pralsetinib plasma concentrations reached steady state by 3 to 5 days. The mean accumulation ratio was approximately 2-fold after once-daily repeated oral administration.
The median time to peak concentration (T_{max}) ranged from 2 to 4 hours following single doses of pralsetinib 60 mg to 600 mg.
Food Effect
Following administration of a single dose of 200 mg Gavreto with a high-fat meal (approximately 800 to 1000 calories with 50 to 60% of calories from fat) the mean (90% CI) C_{max} of pralsetinib was increased by 104% (65%, 153%), the mean (90% CI) AUC_{0-INF} was increased by 122% (96%,152%), and the median T_{max} was delayed from 4 to 8.5 hours, compared to the fasted state.

Distribution

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

Metabolism

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

Elimination

The mean (±standard deviation) plasma elimination half-life (T½) of pralsetinib is 15.7 hours (9.8) following single doses and 20 hours (11.7) following multiple doses of pralsetinib. The mean (CV%) apparent oral clearance (CL/F) of pralsetinib is 10.9 L/h (66%) at steady state.

Excretion

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

Kinetics in specific patient groups

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

Hepatic impairment

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

Preclinical data

Repeated dose toxicity

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

In a 4-week repeat-dose toxicology study in non-human primates, physeal dysplasia in the femur occurred at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. In rats there were findings of increased physeal thickness in the femur and sternum as well as tooth (incisor) abnormalities (fractures, dentin matrix alteration, ameloblast/odontoblast degeneration, necrosis) in both 4- and 13-week studies at doses resulting in exposures similar to the

human exposure (AUC) at the clinical dose of 400 mg. Recovery was not assessed in the 13-week toxicology study, but increased physeal thickness in the femur and incisor degeneration did not show evidence of complete recovery in the 28-day rat study.

Genotoxicity

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

Carcinogenicity

Carcinogenicity studies with pralsetinib have not been conducted.

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

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).

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Store at room temperature (15-25 °C).
Keep the container in the outer carton in order to protect the contents from moisture.
Keep out of the reach of children.

Authorisation number

68182 (Swissmedic).

Packs

Bottle with 120 hard capsules [A]

Marketing authorisation holder

Roche Pharma (Switzerland) Ltd., Basel.

Date of revision of the text

August 2021.