PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Gavreto® 100 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 100 mg pralsetinib.

Sugar free

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Non-Small Cell Lung Cancer (NSCLC)

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

RET-Mutant Medullary Thyroid Cancer (MTC)

Gavreto is indicated for the treatment of adult patients with locally advanced or metastatic *RET*-mutant MTC who require systemic therapy.

RET-Fusion Positive Thyroid Cancer

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

4.2 Posology and method of administration

General

A validated assay is required for the selection of patients with a *RET*-gene fusion (NSCLC or thyroid cancer) or a *RET*-gene mutation (MTC).

Posology

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, patients should take the next dose at the scheduled time.

Dose Modifications

Adverse Reactions

Management of adverse reactions may require temporary interruption, dose reduction, or discontinuation of treatment with Gavreto, based on the medical practitioner'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. 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.
Haemorrhagic 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 haemorrhagic events.
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

Interactions with other Medicinal Products

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. 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 Gavreto with strong CYP3A4 inducers. If coadministration with a strong CYP3A4 inducer cannot be avoided, the dose of Gavreto should be increased to double the current Gavreto dose starting on Day 7 of coadministration of Gavreto 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 Dosage Instructions

Paediatric use

NSCLC

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

RET-Mutant Medullary Thyroid Cancer (MTC) and RET-Fusion Positive Thyroid Cancer

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

Elderly use

No dose adjustment of Gavreto is required in patients ≥ 65 years of age (see section 5.2).

Renal Impairment

No dose adjustment is required in patients with mild and moderate renal impairment. The safety and efficacy of Gavreto have not been studied in patients with severe renal impairment (see section 5.2). Since Gavreto 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 (see section 5.2).

Method of Administration

Gavreto hard capsules should be taken on an empty stomach. Do not to 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.

4.3 Contraindications

Gavreto is contraindicated in patients with a known hypersensitivity to pralsetinib or any of the excipients of Gavreto. Listed in section 6.1.

4.4 Special warnings and precautions for use

General

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).

Hypertension

Hypertension has been reported in clinical trials with Gavreto. Do not initiate Gavreto in patients with uncontrolled hypertension. Optimise 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).

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. See section 4.2 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).

Embryo-Foetal Toxicity

Based on findings from animal studies and its mechanism of action, Gavreto has the potential to cause foetal harm when administered to pregnant women (see section 5.2). 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 sections 4.6 and 5.3).

Female patients of reproductive potential must use effective non-hormonal contraception during treatment with Gavreto and for 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 Special Populations

Paediatric Use

NSCLC

Safety and efficacy in paediatric patients (<18 years) have not been established.

RET-Mutant Medullary Thyroid Cancer (MTC) and RET-Fusion Positive Thyroid Cancer

Safety and efficacy in paediatric patients (<18 years) have not been established.

In nonclinical repeat-dose toxicology studies physeal dysplasia in non-human primates and increased physeal thickness and incisor tooth degeneration in rats were observed at exposures (AUC_{0_24}) similar to clinical exposures at the 400 mg QD dose. Refer to section 5.3 for more details.

4.5 Interaction with other medicines and other forms of interaction

In vitro data indicate that pralsetinib is primarily metabolised by CYP3A4 and transported by P-gp. Therefore, inducers and inhibitors of CYP3A4 and P-gp may alter the plasma concentrations of pralsetinib.

Effects of Other Medicines on Gavreto

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.

Coadministration of pralsetinib with a strong CYP3A4 inhibitor or combined P-gp and strong CYP3A4 inhibitor may increase pralsetinib plasma concentrations and may result in increased adverse reactions. 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).

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.

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

P-gp inhibitors

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Pregnancy testing

Verify the pregnancy status of females of reproductive potential prior to initiating Gavreto.

Contraception

Female patients of reproductive potential must use effective non-hormonal contraception during treatment with Gavreto and for 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.

Pregnancy

Female patients of reproductive potential must be advised to avoid pregnancy while receiving Gavreto (see section 4.4). Patients receiving Gavreto should be advised of the potential hazard to the foetus. Female patients should be advised to contact their doctor, should pregnancy occur.

Breastfeeding

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 breastfeeding during treatment with Gavreto and for 1 week following the final dose.

Fertility

See section 5.3 *Impairment of fertility*.

4.7 Effects on ability to drive and use machines

Caution should be exercised when driving or operating machines as patients may experience fatigue and dizziness while taking Gavreto (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile:

Clinical Trials

Summary of the safety profile

The safety of Gavreto was evaluated in 471 patients treated with 400 mg QD in an open-label, single-arm study ("ARROW"). Patients with *RET*-fusion positive NSCLC, *RET*-mutant medullary thyroid cancer, and other *RET*-altered advanced solid tumours were included in the study. Patients received a starting dose of 400 mg once daily until intolerance to therapy, disease progression, or investigator determination that the patient was no longer benefiting from treatment.

b. Tabulated list of adverse reactions

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 4) are listed by MedDRA 19.1 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 (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000).

Table 4: Summary of adverse drug reactions occurring in patients treated with Gavreto (400 mg QD) in the ARROW study (safety population)

System Organ Class **Adverse reaction**	**Frequency category** **(All Grades)**
Blood and Lymphatic System Disorders	
Anaemia[1]	very common
Neutropenia[2]	very common
Leukopenia[3]	very common
Lymphopenia[4]	very common
Thrombocytopenia[5]	very common
Gastrointestinal disorders	
Constipation	very common
Diarrhoea	very common
Nausea	very common
Abdominal pain[6]	very common
Dry mouth	very common
Vomiting	very common
Stomatitis[7]	common
General Disorders and Administration Site Conditions	
Fatigue[8]	very common
Oedema[9]	very common
Pyrexia	very common
Hepatobiliary Disorders	

Aspartate aminotransferase increased	very common
Alanine aminotransferase increased	very common
Hyperbilirubinaemia	very common
Infection and Infestations	
Pneumonia[10, #]	very common
Urinary tract infection°	very common
Investigations	
Blood alkaline phosphatase increased	very common
Metabolism and Nutrition Disorders	
Hypocalcaemia	very common
Hyperphosphataemia	very common
Hypoalbuminaemia	very common
Hypophosphataemia	very common
Hyponatraemia	very common
Musculoskeletal and Connective Tissue Disorders	
Musculoskeletal pain[11]	very common
Blood creatine phosphokinase increased	very common
Nervous system disorders	
Headache[12]	very common
Dizziness	very common
Taste disorder[12][13]	very common
Renal and Urinary Disorders	
Blood creatinine increased	very common
Respiratory, thoracic and mediastinal disorders	
Cough[14]	very common
Dyspnoea*	very common

Pneumonitis[15]	very common
Skin and subcutaneous tissue disorders	
Rash[16]	very common
Vascular Disorders	
Hypertension[17]	very common
Haemorrhage[18]	very common

[1] Includes the preferred terms: Anaemia, Red blood cell count decreased, Aplastic anaemia, Haematocrit decreased, Haemoglobin decreased

[2] Includes the preferred terms: Neutropenia, Neutrophil count decreased

[3] Includes the preferred terms: Leukopenia, White blood cell count decreased

[4] Includes the preferred terms: Lymphopenia, Lymphocyte count decreased

[5] Includes the preferred terms: Thrombocytopenia, Platelet count decreased

[6] Includes the preferred terms: Abdominal pain, Upper abdominal pain

[7] Includes the preferred terms: Stomatitis, Aphthous ulcer

[8] Includes the preferred terms: Fatigue, Asthenia

[9] Includes the preferred terms: Oedema, Swelling face, Peripheral swelling, Generalised oedema, Oedema peripheral, Face oedema, Periorbital oedema, Eyelid oedema, Swelling, Localised oedema

[10] Includes the preferred terms: Pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia cytomegaloviral, Atypical pneumonia, Lung infection, Pneumonia bacterial, Pneumonia haemophilus, Pneumonia influenza, Pneumonia streptococcal, Pneumonia moraxella, Pneumonia staphylococcal, Pneumonia viral, Pneumonia pseudomonal

[11] Includes the preferred terms: Myalgia, Arthralgia, Pain in extremity, Neck pain, Musculoskeletal pain, Back pain, Musculoskeletal chest pain, Bone pain, Spinal pain, Musculoskeletal stiffness

[12] Includes the preferred terms: Headache, Tension Headache

[13] Includes the preferred terms: Dysgeusia, Ageusia

[14] Includes the preferred terms: Cough, Productive Cough

[15] Includes the preferred terms: Pneumonitis, Interstitial lung disease

[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: Hypertension, Blood pressure increased

[18] Includes the preferred terms identifed using the MedDRA 19.1 SMQ Haemorrhage

° Includes 1 (0,2 %) Grade 5 event

* Includes 2 (0,4 %) Grade 5 events

Includes 10 (1,9 %) Grade 5 events

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Report Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Patients who experience overdose should be closely supervised and supportive care instituted. There is no specific antidote for overdose with Gavreto.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent, protein kinase inhibitors ATC code: L01EX23

Pharmacological classification: A.26 Cytostatic agents

Mechanism of Action

Pralsetinib is a tyrosine kinase inhibitor that targets oncogenic *RET* fusions and mutations, including V804 gatekeeper mutations associated with resistance to other therapies. *In vitro*, pralsetinib inhibited several oncogenic *RET* fusions and mutations (CCDC6 *RET*, *RET* V804L, *RET* V804M and *RET* M918T) with half maximal inhibitory concentrations at clinically relevant concentrations. In a broad

panel of purified enzyme assays, pralsetinib demonstrated selectivity for *RET* with 81-fold selectivity over VEGFR2.

RET fusion proteins and activating point mutations can drive tumourigenic 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.

Cardiac Electrophysiology

The QT interval prolongation potential of pralsetinib was assessed in 34 patients with *RET*-positive solid tumours administered at 400 mg once daily. No clinically relevant mean increase in QTc (i.e.> 20 ms) was detected in the study. No effect on heart rate or cardiac conduction (PR, QRS, and RR intervals) was observed.

Clinical efficacy and safety

The efficacy of pralsetinib was demonstrated in a multi-centre, open-label clinical trial in adults (ARROW). Patients with *RET*-fusion positive NSCLC, thyroid cancer, and other *RET*-altered advanced solid tumours were included in the study.

Efficacy was established on the basis of overall response rate (ORR) according to RECIST v1.1 and duration of response (DOR), as evaluated by a Blinded Independent Central Review (BICR). Additional efficacy outcome measures included disease control rate (DCR) and Clinical Benefit Rate (CBR) also evaluated by a BICR.

Metastatic *RET*-Fusion Positive NSCLC

Metastatic RET Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy

The assessment of efficacy was based on a total of 126 patients with *RET* fusion-positive NSCLC with measurable disease at baseline and sufficient evidence of a *RET* alteration who received prior platinum-based chemotherapy treated with pralsetinib at a starting doses of 400 mg once daily.

In patients with *RET* fusion-positive NSCLC patients who received prior platinum-based chemotherapy, Overall Response Rate (ORR) was 61,9 % (78/126, 95 % CI: 52,8-70,4). The median Duration of Response (DOR) was 22,3 months (95 % CI: 15,1, NE).

Efficacy results for *RET* fusion-positive NSCLC patients who received prior platinum-based chemotherapy are summarised in Table 5.

Table 5: Efficacy Results in ARROW (Metastatic RET Fusion-Positive NSCLC) (MDP)

Efficacy Parameter	**Previously treated with platinum chemotherapy (N=126)**	**Previously treated with systemic treatment (N=148)**	**Treatment-naïve (N=68)**
Overall Response Rate (ORR)[a], % (95 % CI)	61,9 (52.8, 70.4)	63,5 (55.2, 71.3)	79,4 (67.9, 88.3)
Complete Response, %	4,0	3,4	15,9
Partial Response, %	57,9	60,1	73,5
Duration of Response (DOR)	**(N=78)**	**(N=94)**	**(N=54)**
Median, months (95 % CI)	22,3 (15.1-NE)	22,3 (15.1, NE)	NR (9.0, NE)
Patients with DOR ≥ 6 months[b], %	73,1	74,5	55,6

MDP = measurable disease population

NE = not estimable

NR = Not reached

[a] Confirmed overall response rate assessed by BICR

[b] Calculated using the proportion of responders with an observed duration of response at least 6 months or greater

Treatment-naïve RET Fusion-Positive NSCLC

Efficacy was evaluated in 68 patients with treatment-naïve *RET* fusion-positive NSCLC who were not candidates for platinum-based chemotherapy with measurable disease enrolled into ARROW.

In patients with treatment-naïve *RET* fusion-positive NSCLC patients, Overall Response Rate (ORR) was 79,4 % (N=54/68, 95 % CI: 67,9-88,3). The median Duration of Response (DOR) was not reached (95 % CI: 9,0, NE).

Efficacy results for treatment-naïve *RET* fusion-positive NSCLC are summarised in Table 5.

***RET*-Mutant Medullary Thyroid Cancer**

The efficacy of pralsetinib was demonstrated in patients with *RET*-mutant MTC with measurable disease at baseline and sufficient evidence of a *RET* mutation who were treated with pralsetinib at a starting dose of 400 mg QD in a multicentre, open-label, multi-cohort clinical trial (ARROW).

RET-Mutant MTC Previously Treated with Cabozantinib and/or Vandetanib

Efficacy was evaluated in 61 patients with *RET*-mutant advanced MTC previously treated with cabozantinib and/or vandetanib.

Efficacy results for RET-mutant advanced MTC previously treated with cabozantinib and/or vandetanib are summarised in Table 6. The median time to first response was 3,7 months (range: 1,8-12,9 months).

Table 6: Efficacy Results for *RET*-Mutant MTC and *RET*-Fusion Positive Thyroid Cancer (ARROW) (MDP)

	***RET*-Mutant MTC**		**RET fusion-positive thyroid cancer**
	Previously Treated with Cabozantinib and/or Vandetanib	**Treatment-naïve**	
Efficacy Parameters	**(N=61)**	**(N=62)**	**N=20**
Overall Response Rate (ORR)[a], % (95 % CI)	54,1(40.8, 66.9)	77,4 (65.0, 87.1)	85,0 (62.1, 96.8)
Complete Response, %	1,6	6,5	10,0
Partial Response, %	52,5	71,0	75,0
Duration of Response (DOR)	**(N=33)**	**(N=48)**	**N=17**
Median in months (95 % CI)	21,7 (18.0, NE)	NR (NE, NE)	17,5 (11.2, NE)
Patients with DOR ≥ 6 months[b], %	93,9	79,2	94,1

MDP = measurable disease population

NE = Not Estimable

NR = Not Reported

[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

Treatment-naïve RET-Mutant MTC

Efficacy was evaluated in 62 patients with treatment-naïve *RET*-mutant advanced MTC who were not candidates for standard systemic therapies.

Efficacy results for treatment-naïve *RET*-mutant MTC are summarised in Table 6. The median time to first response was 5,6 months (range: 1,6-18,6 months).

***RET* Fusion-Positive Thyroid Cancer**

The efficacy of pralsetinib was demonstrated in 20 *RET* fusion-positive advanced thyroid cancer patients with measurable disease at baseline and sufficient evidence of a RET fusion who were treated with pralsetinib at a starting dose of 400 mg QD in a multicentre, open-label, multi-cohort clinical trial (ARROW, NCT03037385).

Efficacy results are summarised in Table 6. The median time to first response was 1,84 months (range: 1,7-7,9 months).

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 (C_{max}) and area under the concentration-time curve ($AUC_{0\text{-}24h}$) of pralsetinib at 400 mg was 2 470 (55,1 %) ng/mL and 36 700 (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 post dose.

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 standardised 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).

Pralsetinib 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 303 L (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 catalysed by UGT1A4. Following a single oral dose of approximately 310 mg of radiolabelled pralsetinib to healthy subjects, pralsetinib metabolites from oxidation (M531, M453, M549b) and glucuronidation (M709) were detected as 5 % or less.

Elimination

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) [^{14}C]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.

Pharmacokinetics in Special Populations

Paediatric Population

RET-fusion positive thyroid cancer and MTC

Population pharmacokinetic data analysis demonstrated that age and body weight had no clinically meaningful effect on the steady state exposure of pralsetinib, that drug exposure is expected to be similar between adults and paediatric patients age 12 years and older, and that the course of *RET*-mutant MTC and *RET*-fusion thyroid cancer are sufficiently similar in adults and paediatric patients to allow extrapolation of data in adults to paediatric patients.

Geriatric Population

Data obtained in geriatric patients show that pharmacokinetic parameters for pralsetinib are not significantly affected in this population.

Renal impairment

Based on a population pharmacokinetic analysis, pralsetinib 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 pralsetinib 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 pralsetinib, hepatic impairment may result in increased plasma concentrations. Based on a population pharmacokinetic analysis, pralsetinib 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 pralsetinib 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

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.

Impairment of Fertility

In a dedicated fertility and early embryonic development study conducted in treated male rats mated to treated female rats, although pralsetinib did not have clear effects on male or female mating performance or ability to become pregnant, post-implantation loss occurred 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). At the 20 mg/kg dose level (approximately 2,9 times the human exposure (AUC) at the clinical dose of 400 mg based on toxicokinetic data from the 13-week rat toxicology study) 82 % of female rats had totally resorbed litters, with 92 % post-implantation loss (early resorptions). 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.

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 1x the human exposure at the 400 mg once daily dose).

Embryo-Foetal toxicity

In an embryo-foetal 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

Repeat-dose toxicity studies

In 4- and 13-week studies in rats and cynomolgus monkeys, haematological effects were observed in both species at exposures below the human exposure (AUC) at 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 incisor tooth 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. Additional adverse findings at higher exposures included hyperphosphataemia and multi-organ mineralisation in rats (approximately 2 times), and haemorrhage in the heart of preterm decedents (approximately 5,3 times) relative to the human AUC at the clinical dose of 400 mg.

Cardiovascular effects

Increased blood pressure was observed in rats after a single dose of 25 mg/kg (approximately 2-fold the human clinical C_{max} at 400 mg based on the toxicokinetic data at 20 mg/kg from the 28-day rat toxicology study).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

hydroxypropyl methylcellulose

microcrystalline cellulose

sodium bicarbonate

citric acid, anhydrous

magnesium stearate

pregelatinised starch

Capsule shell :

hypromellose

titanium dioxide

FD&C Blue #1 (Brilliant Blue FCF)

Printing ink:

shellac

dehydrated alcohol

isopropyl alcohol

butyl alcohol

propylene glycol

strong ammonia solution

purified water

potassium hydroxide

titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30 °C. Keep the bottle tightly closed in order 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

White, high density polyethylene (HDPE) bottle and white child resistant polypropylene pictorial cap with foil induction seal liner and silica gel dessicant packet.

Pack sizes: 60, 90 or 120 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Disposal of unused/expired medicines

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.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road, Hertford Office Park,

Building E, Vorna Valley, Midrand,

Johannesburg, 1686

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER(S)

56/26/0684

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 17 October 2023

10. DATE OF REVISION OF THE TEXT

Last revision: 17 October 2023