PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrRETEVMO™

Selpercatinib capsules

Capsules, 40 mg and 80 mg, oral

Protein Kinase Inhibitor

RETEVMO™, indicated as monotherapy for the treatment of:

- metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC) in adult patients,
- *RET*-mutant medullary thyroid cancer in adult and pediatric patients 12 years of age and older with unresectable advanced or metastatic disease,
- *RET* fusion-positive differentiated thyroid carcinoma in adult patients with advanced or metastatic disease (not amenable to surgery or radioactive iodine therapy) following prior treatment with sorafenib and/or lenvatinib.

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for RETEVMO™ please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

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What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics	04/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

RETEVMO (selpercatinib) is indicated as monotherapy for the treatment of:

- metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC) in adult patients,
- *RET*-mutant medullary thyroid cancer (MTC) in adult and pediatric patients 12 years of age and older with unresectable advanced or metastatic disease,
- *RET* fusion-positive differentiated thyroid carcinoma in adult patients with advanced or metastatic disease (not amenable to surgery or radioactive iodine therapy) following prior treatment with sorafenib and/or lenvatinib.

Treatment with RETEVMO should only be initiated following confirmation of a *RET* gene fusion or mutation using a validated test (see 14. CLINICAL TRIALS14. CLINICAL TRIALS).

Promising clinical effectiveness of RETEVMO for the above indications is based on objective response rates (ORR) and duration of responses (DOR) from LIBRETTO-001, a multi-center, multi-cohort, open-label, Phase 1/2 trial in patients with specific genetic alterations in *RET* (see 14 CLINICAL TRIALS).

1.1 Pediatrics

Pediatrics (12-17 years of age): Based on the data submitted and reviewed by Health Canada, the promising clinical effectiveness of RETEVMO have been established in adolescent patients 12-17 years of age with unresectable advanced or metastatic *RET*-mutant medullary thyroid cancer (see 7 WARNINGS AND PRECAUTIONS, Special Populations, 7.1.3 Pediatrics [<18 years of age]).

Pediatrics (<12 years of age): The safety and efficacy of RETEVMO in pediatric patients younger than 12 years of age have not been established (see 7 WARNINGS AND PRECAUTIONS, Special Populations, 7.1.3 Pediatrics [<18 years of age]).

1.2 Geriatrics

Geriatrics (≥65 years of age) Of the 702 patients in the safety database who received RETEVMO in LIBRETTO-001, 34% (239 patients) were ≥65 years of age and 10% (67 patients) were ≥75 years of age. No overall differences were observed in the safety or effectiveness of RETEVMO between patients who were ≥65 years of age and younger patients.

2 CONTRAINDICATIONS

RETEVMO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Embryo-Fetal toxicity (see 7 WARNINGS AND PRECAUTIONS, Special Populations, 7.1.1 Pregnant Women)
- Hemorrhage (see 7 WARNINGS AND PRECAUTIONS, Hematologic)
- Hepatoxicity (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic)
- Hypersensitivity (see 7 WARNINGS AND PRECAUTIONS, Immune)
- Hypertension (see 7 WARNINGS AND PRECAUTIONS, Hypertension)
- QTc interval prolongation (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 10 CLINICAL PHARMACOLOGY, Pharmacodynamics, Cardiac Electrophysiology)

RETEVMO should only be prescribed and supervised by a qualified health professional experienced in the use of anti-cancer agents.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Confirm the presence of a *RET* gene fusion (for patients with NSCLC or thyroid cancer) or a *RET* gene mutation (for patients with MTC) using a validated test before starting treatment with RETEVMO.
- Patient blood pressure is to be optimized before starting RETEVMO.
- Reduce RETEVMO dose in patients with severe hepatic impairment (see 4.2 Recommended Dose and Dosage Adjustment).

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage of RETEVMO is based on body weight:

- Less than 50 kg: 120 mg twice daily
- 50 kg or greater: 160 mg twice daily

RETEVMO is administered orally approximately every 12 hours until disease progression or unacceptable toxicity.

Patients with severe hepatic impairment (Child-Pugh C) (less than 50 kg or 50 kg or greater) should receive a reduced dose of 80 mg twice daily (see 10 CLINICAL PHARMACOLOGY, Special Populations) and monitor ALT and AST more frequently as clinically indicated.

Health Canada has not authorized an indication for use in children <12 years of age (see 1 INDICATIONS).

Table 1 provides dose modifications for QT interval prolongation, increased aspartate aminotransferase (AST) or alanine aminotransferase (ALT), hypersensitivity, hypertension, hemorrhagic events and other Grade 3 or 4 adverse reactions.

The RETEVMO dosage recommendations per dose reduction level, for the management of these adverse reactions, are provided in Table 2. Permanently discontinue RETEVMO in patients unable to tolerate the third dose reduction level.

Table 1 - Recommended RETEVMO Dosage Modifications for Adverse Reactions

Event	Grade*	Dose Modification
QT Interval Prolongation	Grade 3	• Withhold RETEVMO until toxicity resolves to baseline or Grade 1. • Resume RETEVMO at a reduced dose by 1 dose level. • Permanently discontinue if QT prolongation remains uncontrolled after 2 dose reductions.
	Grade 4 or if patient has signs or symptoms of serious arrhythmia	• Permanently discontinue RETEVMO.
AST/ALT Increase	Grade 3 and Grade 4	• Withhold RETEVMO and perform AST/ALT monitoring once weekly until resolution to Grade 1 or baseline. • Resume RETEVMO at a reduced dose by 2 dose levels and monitor AST/ALT once weekly. • RETEVMO may be increased by 1 dose level after a minimum of 2 weeks without recurrence of increased AST/ALT. • Increase to dose taken prior to the onset of Grade 3 or 4 ALT/AST increase after a minimum of 4 weeks without recurrence. Continue AST/ALT monitoring once weekly for 4 weeks thereafter. • Permanently discontinue RETEVMO if recurrence of ≥Grade 3 toxicity despite dose reductions.
Hypersensitivity	All Grades	• Hold RETEVMO until toxicity resolves and begin steroid treatment. • Upon resolution of the event, resume RETEVMO at a reduced dose by 3 dose levels while continuing steroid treatment. • If after 1 week RETEVMO is tolerated without recurrent hypersensitivity, increase RETEVMO by 1 dose level weekly, ensuring that RETEVMO is tolerated for at least 1 week before proceeding to the next dose level. • Taper steroid dose after RETEVMO has been tolerated for at least 7 days at the final dose. • Permanently discontinue RETEVMO if recurrence of toxicity despite dose reductions.

Event	Grade*	Dose Modification
Hypertension	Grade 3	• Hold RETEVMO until hypertension is controlled with medical management. • When controlled, resume RETEVMO at next lower dose level.
	Grade 4	• Discontinue RETEVMO.
Hemorrhagic Events	Grade 3 or Grade 4	• Withhold RETEVMO until recovery to baseline or Grade 0 or 1. • Discontinue RETEVMO for severe or life-threatening hemorrhagic events.
Other Adverse Reactions	Grade 3 or Grade 4	• Withhold RETEVMO until recovery to baseline or Grade 0 or 1. • Resume at a reduced dose.

*Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

Table 2 - Recommended RETEVMO Dosage per Dose Reduction Level for the Management of Adverse Reactions

Dose Reduction levels	Recommended RETEVMO Dosage	
	Patients Weighing Less Than 50 kg	Patients Weighing 50 kg or Greater
First	80 mg orally twice daily	120 mg orally twice daily
Second	40 mg orally twice daily	80 mg orally twice daily
Third	40 mg orally **once** daily	40 mg orally twice daily

Dosage Modifications for Concomitant Use of Strong or Moderate CYP3A4 Inhibitors

Avoid concomitant use of strong or moderate CYP3A4 inhibitors with RETEVMO. If concomitant use of a strong or moderate CYP3A4 inhibitor cannot be avoided, reduce the current RETEVMO dose as recommended in Table 3 and monitor the QTc interval more frequently with ECGs. After the inhibitor has been discontinued for 3 to 5 elimination half-lives of the inhibitor, resume RETEVMO at the dose taken before starting the CYP3A4 inhibitor (see 9.4 Drug-Drug Interactions and 10.3 Pharmacokinetics).

Table 3 - Recommended RETEVMO Dosage for Concomitant Use of Strong or Moderate CYP3A Inhibitors

Current RETEVMO Dosage	Recommended RETEVMO Dosage	
	With a Moderate CYP3A Inhibitor	With a Strong CYP3A Inhibitor
120 mg orally twice daily	80 mg orally twice daily	40 mg orally twice daily
160 mg orally twice daily	120 mg orally twice daily	80 mg orally twice daily

There is no data on the safety of concomitant use of CYP3A inhibitors in patients whose RETEVMO dose was previously reduced due to adverse reactions.

Dosage Modifications for Concomitant Use of Acid-Reducing Agents

Avoid concomitant use of a proton pump inhibitor, a histamine-2 (H2) receptor antagonist, or a locally acting antacid with RETEVMO (see 9.4 Drug-Drug Interactions). If concomitant use cannot be avoided,

- RETEVMO should be taken with food when co-administered with a proton pump inhibitor.
- RETEVMO should be taken 2 hours before or 10 hours after administration of an H2 receptor antagonist.
- RETEVMO should be taken 2 hours before or 2 hours after administration of a locally acting antacid.

4.4 Administration

RETEVMO can be taken with or without food unless coadministered with a proton pump inhibitor (see 4.2 Recommended Dose and Dosage Adjustment).

Patients should swallow the capsules whole and should not open, crush, or chew the capsule.

4.5 Missed Dose

If the patient misses a dose of RETEVMO, the patient should take the next dose at the next scheduled time, unless it is more than 6 hours until the next scheduled dose.

If the patient vomits after taking a dose of RETEVMO, the patient should not take an additional dose. The patient should take the next dose at the next scheduled time. The patient should not take 2 doses at the same time to make up for the missed dose.

5 OVERDOSAGE

There is no known antidote for RETEVMO. The treatment of overdose of RETEVMO should consist of general supportive measures. ECG monitoring is recommended.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION, AND PACKAGING

Table 4 - RETEVMO Dosage Forms, Strengths, Composition, and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	capsule 40 mg, 80 mg	Black iron oxide, colloidal silicon dioxide, FD & C Blue No. 1 (80 mg capsule only), gelatin, microcrystalline cellulose, pharmaceutical grade printing ink, titanium dioxide

RETEVMO (selpercatinib) is supplied as grey (40 mg) and blue (80 mg) hard capsules.

The 40 mg capsules are grey opaque hard gelatin capsules (size 2) with black printing of “Lilly 3977” and “40 mg” on the body of the capsule. They are supplied in 75 mL bottles of 60 capsules.

The 80 mg capsules are blue opaque hard gelatin capsules (size 0) with black printing of “Lilly 2980” and “80 mg” on the body of the capsule. They are supplied in 125 mL bottles of 60 capsules and 190 mL bottles of 120 capsules.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Cardiovascular

QTc Interval Prolongation: RETEVMO causes concentration-dependent QTc interval prolongation (see 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data). QTc interval prolongation can lead to an increased risk of ventricular arrhythmias including torsade de pointes. The use of RETEVMO should be avoided in patients with conditions that may increase the risk of experiencing torsade de pointes.

Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender, age ≥65 years, baseline prolongation of the QTc interval, presence of genetic variants affecting cardiac ion channels or regulatory proteins (especially congenital long QT syndromes), family history of sudden cardiac death at <50 years of age, cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease), history of arrhythmias, electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia), conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders), bradycardia, acute neurological events (e.g., intracranial or subarachnoid hemorrhage, stroke, intracranial trauma), diabetes mellitus, and autonomic neuropathy.

Combination use of RETEVMO with other drugs known to prolong the QTc interval and/or strong or moderate CYP3A inhibitors should be avoided, as this may lead to further prolongation of the QTc interval. Use caution if RETEVMO is administered in combination with agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) or drugs that can decrease electrolytes (see 9 DRUG INTERACTIONS). Monitor the QTc interval more frequently in these patients (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Patients must have a QTcF interval of ≤470 ms and serum electrolytes within normal range before starting RETEVMO treatment. Perform electrocardiograms and measure serum electrolytes before starting RETEVMO treatment and during treatment. Treatment with RETEVMO should be avoided in patients with uncorrected hypokalemia, hypomagnesemia, or hypocalcemia (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Interruption and dose reduction or permanent discontinuation of RETEVMO may be required based on the severity of QTc interval prolongation (see 4.2 Recommended Dose and Dosage Adjustment).

Hypertension: Hypertension occurred in 35% of patients in LIBRETTO-001, including Grade 3 or 4 hypertension in 18% of patients (see 8 ADVERSE REACTIONS). Treatment-emergent hypertension was most commonly managed through concomitant anti-hypertension medications.

Patient blood pressure is to be optimized before starting RETEVMO. Monitor blood pressure during RETEVMO treatment. Based on the level of increased blood pressure, RETEVMO may require dose modification (see 4.2 Recommended Dose and Dosage Adjustment). Permanently discontinue RETEVMO if medically significant hypertension cannot be controlled with antihypertensive therapy.

Driving and Operating Machinery

RETEVMO may influence the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines in case they experience fatigue or dizziness during treatment with RETEVMO.

Hematologic

Serious, including fatal, hemorrhagic events can occur with RETEVMO. Grade ≥3 hemorrhagic events occurred in 2.3% of patients treated with RETEVMO, including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis.

Permanently discontinue RETEVMO in patients with severe or life-threatening hemorrhage.

Hepatic/Biliary/Pancreatic

Serious hepatic adverse reactions occurred in 2.7% of patients treated with RETEVMO in the LIBRETTO-001 study (see 8 ADVERSE REACTIONS). Increased AST occurred in 51% of patients, including Grade 3 or 4 events in 8%. Increased ALT occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and for increased ALT, it was 4.1 weeks (range: 6 days to 1.5 years).

Monitor ALT and AST before starting RETEVMO, every 2 weeks during the first 3 months of treatment, then monthly thereafter and as clinically indicated. Withhold, reduce dose, or permanently discontinue RETEVMO based on the severity of ALT/AST increase (see 4.2 Recommended Dose and Dosage Adjustment and 8 ADVERSE REACTIONS).

Immune

Hypersensitivity occurred in 4.3% of patients receiving RETEVMO, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range: 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash, and arthralgias or myalgias with concurrent decreased platelets or AST/ALT increase.

If hypersensitivity occurs, withhold RETEVMO until toxicity resolves and begin steroid treatment. Upon resolution of the event, resume RETEVMO at a reduced dose by 3 dose levels for 1 week. If tolerated without recurrent hypersensitivity, increase RETEVMO by 1 dose level weekly. Continue steroid treatment until the target dose is reached and then taper (see 4.2 Recommended Dose and Dosage Adjustment). Permanently discontinue RETEVMO if toxicity recurs despite dose reductions.

Impaired Wound Healing

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, RETEVMO has the potential to adversely affect wound healing.

Withhold RETEVMO for at least 7 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 RETEVMO after resolution of wound healing complications has not been established.

Monitoring and Laboratory Tests

Perform electrocardiograms and measure serum electrolytes before starting RETEVMO treatment. Ensure a QTcF interval of ≤470 ms before starting RETEVMO treatment. Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to initiation or continuation of RETEVMO treatment. Monitor electrocardiograms and serum electrolytes in all patients after 1 week of RETEVMO treatment, at least monthly for the first 6 months of RETEVMO treatment, and otherwise as clinically indicated. Monitor the QTc interval more frequently in patients who are at an increased risk of torsade de pointes (see 7 WARNINGS AND PRECAUTIONS, QTc Interval Prolongation), and adolescent patients <50 kg (see 7.1.3 Pediatrics [<18 years of age]). Monitor the QTc interval more frequently if RETEVMO is concomitantly administered with strong or moderate CYP3A inhibitors or drugs known to prolong the QTc interval (see 9.4 Drug-Drug Interactions).

Control hypertension before starting RETEVMO. Monitor blood pressure after 1 week of starting therapy, monthly for 6 months, and as clinically indicated (see 4.1 Dosing Considerations).

Monitor ALT and AST before starting RETEVMO, every 2 weeks during the first 3 months of treatment, then monthly thereafter and as clinically indicated (see 4.2 Recommended Dose and Dosage Adjustment).

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.

Sexual Health

Reproduction: Women of childbearing potential must be advised to avoid becoming pregnant while receiving RETEVMO.

Advise females of reproductive potential to use highly effective contraception during treatment with RETEVMO and for at least 2 weeks after the last dose.

Verify negative pregnancy status in women of reproductive potential before starting RETEVMO.

Advise men with female partners with reproductive potential to use effective contraception during treatment and for at least 2 weeks after the last dose of RETEVMO (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

Fertility: RETEVMO may impair fertility in men and women of reproductive potential (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) occurred in 1% of patients with medullary thyroid carcinoma receiving RETEVMO. 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, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

7.1 Special Populations

7.1.1 Pregnant Women

RETEVMO should not be used during pregnancy. Based on findings in animals and its mechanism of action, RETEVMO can cause fetal harm when administered to a pregnant woman. In an embryo-fetal development study in rats during organogenesis, selpercatinib was teratogenic and caused embryolethality and malformations at maternal exposures that were approximately equal to the exposure of the recommended human dose (AUC) (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

7.1.2 Breast-Feeding

There are no data on the presence of selpercatinib in human milk, effects of selpercatinib on the breastfed child, or the effects of selpercatinib on milk production. Because of the potential for serious adverse reactions in breastfed children, advise a nursing woman to discontinue breastfeeding during RETEVMO treatment and for at least 2 weeks after the last dose of RETEVMO.

7.1.3 Pediatrics (<18 years of age)

In the LIBRETTO-001 study, there were no adolescent patients with RET fusion-positive thyroid cancer and only 3 adolescent patients (15, 16 and 17 years of age) with advanced or metastatic *RET*-mutant medullary thyroid cancer. No unexpected safety findings were observed in these pediatric patients compared to the adult population.

RETEVMO is associated with a potential risk for delayed growth. In non-clinical studies, animals showed signs of physeal hypertrophy and tooth dysplasia at doses resulting in exposures of approximately 3 times (for rats) and approximately 0.3 times (for minipigs) the human exposure at the 160 mg twice daily clinical dose. In juvenile rats, epiphyseal growth plate changes were associated with decreased femur length and reductions in bone mineral density that were not reversible (see 16 NON-CLINICAL TOXICOLOGY). These observations may be relevant to pediatric patients with open growth plates. 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.

RETEVMO may impair fertility in adolescents of reproductive potential. (see 16 NON-CLINICAL TOXICOLOGY, Reproductive Toxicology).

The safety of long-term use of RETEVMO in adolescent patients has not been evaluated.

The safety and efficacy of RETEVMO in patients under the age of 12 has not been established.

Reduce the RETEVMO dose in adolescent patients <50 kg (see 4 DOSAGE AND ADMINISTRATION) and monitor the QTc interval more frequently with ECGs.

7.1.5 Patients with Hepatic Impairment

Limited safety data are available for the use of RETEVMO in patients with severe hepatic impairment. Patients with severe hepatic impairment should receive a reduced dose of

RETEVMO (see 4 DOSAGE AND ADMINISTRATION) and monitor ALT and AST more frequently as clinically indicated.

7.1.6 Patients with Renal Impairment

The use of RETEVMO in patients with end-stage renal disease is not recommended (see 10 ACTION AND CLINICAL PHARMACOLOGY– Special Populations and Conditions).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most commonly reported adverse reactions, including laboratory abnormalities (≥25%), in order of decreasing frequency were: increased AST, increased ALT, lymphocyte count decreased, glucose increased, leukocytes decreased, albumin decreased, calcium decreased, dry mouth, creatinine increased, diarrhea, alkaline phosphatase increased, hypertension, platelets decreased, total cholesterol increased, fatigue, rash, sodium decreased and constipation.

Serious adverse events occurred in 33% of patients who received RETEVMO. The most frequent serious adverse events (in ≥2% of patients) were pneumonia and hemorrhage (see Table 5, footnote c for list of terms that contributed to the hemorrhage composite term).

Deaths due to an adverse event occurred in 3% of patients; events that occurred in >1 patient included sepsis (n=3), cardiac arrest (n=3), respiratory failure (n=3), and hemorrhage (n=3).

Permanent discontinuation due to an adverse event occurred in 5% of patients who received RETEVMO. Adverse events resulting in permanent discontinuation included: increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%).

Dosage interruptions due to an adverse event occurred in 42% of patients who received RETEVMO. Adverse events requiring dosage interruption in >2% of patients included: ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation.

Dose reductions due to an adverse event occurred in 31% of patients who received RETEVMO. Adverse events requiring dosage reductions in >2% of patients included: ALT increased, AST increased, QT prolongation, and fatigue.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

The safety of RETEVMO has been assessed in 702 patients from an open-label, multi-center, multi-cohort, single-arm, phase 1/2 study (LIBRETTO-001). The median age was 59 years (range: 15 to 92 years); 0.4% were pediatric patients less than 18 years of age; 52% were male; and 69% were White, 22% were Asian, 5% were Hispanic/Latino, and 3% were Black. ECOG performance status was 0-1 (95%) or 2 (5%). Patients with hepatic, renal or cardiac impairment (including prolonged QT syndrome) at baseline were not included in LIBRETTO-001. Most patients had metastatic *RET*-altered solid tumors, including *RET* fusion-positive non-small cell lung cancer (n=329); *RET*-mutant medullary thyroid cancer (n=299) and *RET* fusion-positive advanced thyroid cancer (n=37). RETEVMO was evaluated as a single agent at

160 mg orally twice daily. Ninety-five percent (95%) of patients received at least one dose of RETEVMO at the recommended dosage of 160 mg orally twice daily. Patients received RETEVMO for a median duration of 8.7 months (range: 0.1-31.0 months).

Treatment-emergent adverse events reported in ≥10% of patients treated with RETEVMO in LIBRETTO-001 are listed in Table 5.

Table 5 - Treatment-Emergent Adverse Events (TEAEs) Occurring in ≥10% of Patients Treated with RETEVMO in LIBRETTO-001

System Organ Class Preferred Term[a]	RETEVMO N=702	
	All Grades[b] n (%)	Grade 3 or 4 n (%)
Blood and Lymphatic Disorders		
Hemorrhage[c]	104 (14.8)	13 (1.9)
Thrombocytopenia	94 (13.4)	18 (2.6)
Leukopenia	71 (10.1)	7 (1.0)
Lymphopenia	71 (10.1)	29 (4.1)
Gastrointestinal Disorders		
Dry Mouth	272 (38.7)	0
Diarrhea	254 (36.2)	24 (3.4)
Constipation	178 (25.4)	4 (0.6)
Nausea	159 (22.6)	4 (0.6)
Abdominal pain[d]	161 (22.9)	13 (1.9)
Vomiting	106 (15.1)	2 (0.3)
General Disorders and Administrative Site Conditions		
Edema[e]	242 (34.5)	2 (0.3)
Fatigue[f]	246 (35.0)	14 (2.0)
Pyrexia	95 (13.5)	1 (0.1)
Infections and Infestations		
Urinary tract infection	79 (11.3)	9 (1.3)
Investigations		
AST increased	210 (29.9)	52 (7.4)
ALT increased	201 (28.6)	64 (9.1)
Blood creatinine increased	136 (19.4)	1 (0.1)
ECG QT prolonged	116 (16.5)	28 (4.0)
Blood alkaline phosphatase increased	79 (11.3)	8 (1.1)
Metabolism and Nutrition Disorders		
Decreased appetite	82 (11.7)	1 (0.1)

System Organ Class Preferred Term[a]	RETEVMO N=702	
	All Grades[b] n (%)	Grade 3 or 4 n (%)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	92 (13.1)	0
Back pain	82 (11.7)	5 (0.7)
Nervous System Disorders		
Headache	161 (22.9)	10 (1.4)
Dizziness	82 (11.7)	0
Respiratory, Thoracic, and Mediastinal Disorders		
Cough[g]	127 (18.1)	0
Dyspnea[h]	115 (16.4)	16 (2.3)
Skin and Subcutaneous Tissue Disorders		
Rash[i]	191 (27.2)	5 (0.7)
Dry skin	82 (11.7)	0
Vascular Disorders		
Hypertension	246 (35.0)	123 (17.5)

[a] Reported adverse event terms were coded using MedDRA (version 21.0).

[b] The severity of TEAEs was graded based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 4.03.

[c] Hemorrhage includes epistaxis, hematuria, hemoptysis, contusion, rectal hemorrhage, vaginal hemorrhage, ecchymosis, hematochezia, petechiae, traumatic hematoma, anal hemorrhage, blood blister, blood urine present, cerebral hemorrhage, gastric hemorrhage, hemorrhage intracranial, spontaneous hematoma, abdominal wall hematoma, angina bullosa hemorrhagica, diverticulum intestinal hemorrhagic, eye hemorrhage, gastrointestinal hemorrhage, gingival bleeding, hematemesis, intraabdominal hemorrhage, lower gastrointestinal hemorrhage, melena, mouth hemorrhage, post procedural hemorrhage, pelvic hematoma, periorbital hematoma, pharyngeal hemorrhage, pulmonary contusion, purpura, retroperitoneal hematoma, subarachnoid hemorrhage, subdural hemorrhage, upper gastrointestinal hemorrhage, vessel puncture site hematoma.

[c] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain.

[e] Edema includes edema, edema peripheral, face edema, periorbital edema, eye edema, eyelid edema, orbital edema, localized edema, lymphedema, scrotal edema, peripheral swelling, scrotal swelling, swelling, swelling face, eye swelling.

[f] Fatigue includes fatigue, asthenia, malaise.

[g] Cough includes cough, productive cough.

[h] Dyspnea includes dyspnea, dyspnea exertional, dyspnea at rest.

[i] Rash includes rash, rash erythematous, rash macular, rash maculopapular, rash morbilliform, rash pruritic.

8.3 Less Common Clinical Trial Adverse Reactions

Additional less common treatment-emergent adverse events (all grades) occurring at an overall incidence <10% and ≥1% of patients included:

Blood and lymphatic system disorders: anemia, neutropenia.

Cardiac disorders: atrial fibrillation, bradycardia, palpitations, pericardial effusion, sinus bradycardia, sinus tachycardia, tachycardia.

Ear and labyrinth disorders: tinnitus, vertigo.

Endocrine disorders: hyperthyroidism, hypothyroidism.

Eye disorders: dry eye, vision blurred.

Gastrointestinal disorders: abdominal distension, ascites, colitis, dysphagia, dyspepsia, enteritis, flatulence, gastritis, gastroesophageal reflux disease, mouth ulceration, stomatitis.

General disorders and administration site conditions: chest discomfort, chest pain, chills, gait disturbance, influenza-like illness, non-cardiac chest pain, mucosal inflammation, pain.

Hepatobiliary disorders: hyperbilirubinemia.

Immune system disorders: hypersensitivity, seasonal allergy.

Infections and infestations: bronchitis, conjunctivitis, diverticulitis, gastroenteritis, lung infection, nasopharyngitis, oral candidiasis, paronychia, pharyngitis, pneumonia, sepsis, sinusitis, skin infection, tooth infection, upper respiratory tract infection.

Injury, poisoning and procedural complications: fall.

Investigations: blood alkaline phosphatase increased, blood bilirubin increased, blood cholesterol increased, blood creatinine increased, blood lactate dehydrogenase increased, blood magnesium decreased, blood phosphorus increased, blood pressure increased, blood thyroid stimulating hormone increased, gamma-glutamyltransferase increased, lipase increased, liver function test increased, protein total decreased, weight decreased, weight increased, transaminases increased.

Metabolism and nutrition disorders: dehydration, hypercalcemia, hypercholesterolemia, hyperglycemia, hyperkalemia, hypernatremia, hyperphosphatemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, vitamin D deficiency.

Musculoskeletal and connective tissue disorders: bone pain, flank pain, muscle spasms, muscular weakness, musculoskeletal chest pain, musculoskeletal stiffness, myalgia, neck pain, pain in extremity.

Neoplasms benign, malignant and unspecified: cancer pain.

Nervous system disorders: amnesia, disturbance in attention, dysgeusia, hypoasthesia, memory impairment, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, presyncope, seizure, syncope, tremor.

Psychiatric disorders: anxiety, confusional state, delirium, depression, insomnia, libido decreased.

Renal and urinary disorders: acute kidney injury, dysuria, micturition urgency, pollakiuria, proteinuria, renal failure, urinary incontinence, urinary retention.

Reproductive system and breast disorders: erectile dysfunction.

Respiratory, thoracic and mediastinal disorders: dysphonia, hypoxia, nasal congestion, nasal dryness, oropharyngeal pain, pleural effusion, pneumonitis, pulmonary embolism, respiratory failure, rhinitis allergic, sinus congestion, upper-airway cough syndrome.

Skin and subcutaneous tissue disorders: acne, alopecia, dermatitis acneiform, eczema, erythema, hyperhidrosis, night sweats, palmar-plantar erythrodysesthesia syndrome, photosensitivity reaction, pruritus, skin exfoliation, skin lesion, skin ulcer.

Vascular disorders: embolism, flushing, hot flush, hypotension.

Additional Adverse Drug Reactions from Clinical Trials: chylothorax (1.4%) and chylous ascites (1.4%) have been observed in selpercatinib-treated patients in ongoing trial LIBRETTO-001 (N=807). In most cases, the event onset latency was more than 1 year.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

The following table (Table 6) provides treatment-emergent shifts from baseline in laboratory abnormalities occurring in patients treated with RETEVMO in the LIBRETTO-001 study.

Table 6 - Laboratory Abnormalities Worsening from Baseline in ≥15% of Patients Treated with RETEVMO in LIBRETTO-001

	RETEVMO[a]	
Laboratory Abnormality[b]	**All Grades n (%)**	**Grade 3 or 4 n (%)**
Chemistry		
Increased AST	352 (51)	52 (8)
Increased ALT	309 (45)	63 (9)
Increased glucose	305 (44)	15 (2)
Decreased albumin	292 (42)	5 (1)
Decreased calcium	285 (41)	26 (4)
Increased creatinine	258 (37)	7 (1)
Increased alkaline phosphatase	248 (36)	16 (2)
Increased total cholesterol	208 (31)	1 (0.1)
Decreased sodium	187 (27)	50 (7)
Decreased magnesium	167 (24)	4 (1)
Increased potassium	165 (24)	8 (1)
Increased bilirubin	158 (23)	14 (2)
Decreased glucose	150 (22)	5 (1)
Hematology		
Decreased lymphocytes	297 (44)	99 (15)
Decreased white blood	294 (43)	11 (2)

cells		
Decreased platelets	230 (33)	19 (3)
Decreased neutrophil count	131 (19)	17 (3)
Decreased hemoglobin	131 (19)	6 (1)

[a] Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 670 to 692 patients.

[b] The severity of TEAEs was graded based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 4.03, except for increased creatinine, which was based on v5.0.

Electrocardiograms: QTc interval prolongation was reported in patients receiving RETEVMO in clinical trials. In the LIBRETTO-001 trial, the mean change from baseline QTcF averaged 18-22 ms at 2 h post-dosing from day 8 of treatment onward in patients initiated at the 160 mg twice daily dose of RETEVMO. Treatment-emergent QTcF values >480 ms and >500 ms were reported in 16.9% and 6.1% of patients, respectively. QTcF increases from baseline >60 ms were reported in 15.4% of patients (see 7 WARNINGS AND PRECAUTIONS and 10.2 Pharmacodynamics).

Treatment with selpercatinib 160 mg BID was also associated with decreases from baseline in heart rate that averaged about -5 bpm to -9 bpm and increases from baseline in the PR interval that averaged about 5 ms to 9 ms from day 8 onward at 2 h post-dosing.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Selpercatinib is a substrate of CYP3A4 and it is predominantly metabolized by CYP3A4.

Coadministration of RETEVMO with a moderate or strong CYP3A4 inhibitor may increase selpercatinib plasma concentrations, which may increase the risk of adverse reactions related to RETEVMO, including QTc interval prolongation.

Coadministration of RETEVMO with a moderate or strong CYP3A4 inducer may decrease selpercatinib plasma concentrations.

Coadministration of RETEVMO with CYP3A4-sensitive substrates may increase plasma concentrations of the CYP3A4 substrates. Coadministration of RETEVMO with sensitive CYP2C8 substrates may increase plasma concentrations of the CYP2C8 substrates.

Selpercatinib inhibits the renal transporter multidrug and toxin extrusion protein 1 (MATE1). In vivo interactions of selpercatinib with clinically relevant substrates of MATE1, such as creatinine, may occur. RETEVMO may increase serum creatinine due to inhibition of the renal tubular secretion transporter MATE1, without affecting glomerular function.

Selpercatinib is an in vitro substrate and inhibitor of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP).

Concomitant use of RETEVMO with P-gp substrates increases their plasma concentrations, which may increase the risk of adverse reactions related to these substrates (see 9.4 Drug-Drug Interactions).

Concomitant use of RETEVMO with acid-reducing agents may decrease selpercatinib plasma concentrations, which may reduce RETEVMO anti-tumor activity.

9.4 Drug-Drug Interactions

The effects of other drugs on RETEVMO are listed in Table 7. The effects of RETEVMO on other drugs are listed in Table 8. The drugs listed in these tables are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction. This list is not exhaustive.

Table 7 - Effects of Other Drugs on RETEVMO

Common Name	Source of Evidence	Effect	Clinical Comment
Drugs that may increase selpercatinib plasma concentrations			
Strong CYP3A4 inhibitors, including but not limited to itraconazole, clarithromycin, voriconazole, ketoconazole, ritonavir, telithromycin, posaconazole	CT, T	Coadministration of multiple doses of itraconazole (200 mg QD) with a single dose of selpercatinib 160 mg increased the selpercatinib $AUC_{0\text{-}INF}$ by 133% and C_{max} by 30%.	Concomitant use of RETEVMO with a strong CYP3A4 inhibitor may increase the risk of adverse reactions associated with RETEVMO, including QTc interval prolongation. Avoid coadministration of RETEVMO with strong CYP3A4 inhibitors. If coadministration cannot be avoided, reduce the current RETEVMO dose (see 4 DOSAGE AND ADMINISTRATION) and monitor the QTc interval more frequently with ECGs.

Moderate CYP3A4 inhibitors, including but not limited to diltiazem, fluconazole, verapamil, ciprofloxacin	T	Coadministration of multiple doses of diltiazem (60 mg TID), fluconazole (200 mg QD), or verapamil (80 mg TID) with multiple doses of selpercatinib (160 mg BID) is predicted by modelling to increase the selpercatinib AUC by 60-99% and C_{max} by 46-76%.	Concomitant use of RETEVMO with a moderate CYP3A inhibitor may increase the risk of adverse reactions associated with RETEVMO, including QTc interval prolongation. Avoid coadministration of RETEVMO with moderate CYP3A4 inhibitors. If coadministration cannot be avoided, reduce the current RETEVMO dose (see 4 DOSAGE AND ADMINISTRATION) and monitor the QTc interval more frequently with ECGs.
Drugs that may decrease selpercatinib plasma concentrations			
Strong CYP3A4 inducers, including but not limited to rifampin, phenytoin, phenobarbital, carbamazepine, dexamethasone, rifabutin	CT, T	Coadministration of multiple doses of rifampin 600 mg QD with a single dose of selpercatinib 160 mg decreased the selpercatinib AUC_{0-INF} by 87% and C_{max} by 70%.	Concomitant use of RETEVMO with a strong CYP3A inducer may reduce RETEVMO anti-tumor activity. Avoid coadministration of RETEVMO with strong CYP3A4 inducers.
Moderate CYP3A4 inducers, including but not limited to bosentan, efavirenz	T	Coadministration of multiple doses of bosentan (62.5 mg BID or 125 mg BID) or efavirenz (600 mg QD) with multiple doses of selpercatinib (160 mg BID) is predicted by modelling to decrease the selpercatinib AUC by 40-70%, and C_{max} by 34-57%.	Concomitant use of RETEVMO with a moderate CYP3A inducer may reduce RETEVMO anti-tumor activity. Avoid coadministration of RETEVMO with moderate CYP3A4 inducers.

Weak CYP3A4 inducers, including but not limited to modenafil	T	Coadministration of multiple doses of modenafil (200 mg QD) with multiple doses of selpercatinib (160 mg BID) is predicted to decrease the selpercatinib AUC by 33%, and C_{max} by 26%.	The combination is not predicted to have any clinical effects.
Proton pump inhibitors (PPIs, including but not limited to omeprazole)	CT	Coadministration with multiple daily doses of omeprazole (40 mg QD) with a single dose of selpercatinib (160 mg) decreased selpercatinib $AUC_{0\text{-}INF}$ by 69% and C_{max} by 88% when RETEVMO was administered fasting. Coadministration with multiple daily doses of omeprazole (40 mg QD) with a single dose of selpercatinib (160 mg) after low-fat or high-fat meal did not significantly change the selpercatinib $AUC_{0\text{-}INF}$ while the C_{max} decreased by 22% to 49%.	Avoid concomitant administration of a proton pump inhibitor with RETEVMO. If concomitant use cannot be avoided, patients should be advised to take RETEVMO with food when coadministered with a proton pump inhibitor.

Histamine-2 (H2) receptor antagonists (including but not limited to ranitidine)	CT, T	Selpercatinib has pH-dependent solubility, with decreased solubility at higher pH. H2 receptor antagonists may interfere with selpercatinib bioavailability. No clinically significant differences in selpercatinib pharmacokinetics were observed when coadministered with multiple daily doses of ranitidine (150 mg BID) given 10 hours prior to and 2 hours after the RETEVMO dose (160 mg BID, administered fasting). Selpercatinib $AUC_{0\text{-}INF}$ decreased by 7% and C_{max} by 18% on co-administration.	Avoid concomitant administration of a H2 receptor antagonist. If concomitant use cannot be avoided, patients should be advised to take RETEVMO 2 hours before or 10 hours after administration of an H2 receptor antagonist.
Locally acting antacids (including but not limited to calcium carbonate)	T	Selpercatinib has pH-dependent solubility, with decreased solubility at higher pH. Locally acting antacids may interfere with selpercatinib bioavailability.	Avoid concomitant administration of a locally acting antacid If concomitant use cannot be avoided, patients should be advised to take RETEVMO 2 hours before or 2 hours after administration of a locally acting antacid.

Legend: CT=Clinical Trial; T=Theoretical.

Table 8 – Effects of RETEVMO on Other Drugs

Common Name	Source of Evidence	Effect	Clinical Comment
Effect of selpercatinib on sensitive CYP2C8 substrates			
Sensitive CYP2C8 substrates, including but not limited to repaglinide, enzalutamide, paclitaxel, sorafenib, rosiglitazone, pioglitazone, montelukast, selexipag, buprenorphine	CT, T	Coadministration of multiple doses of RETEVMO (160 mg BID) with single dose of repaglinide (0.5 mg QD) increased the repaglinide $AUC_{0\text{-}INF}$ by 188% and C_{max} by 91%.	Avoid coadministration of RETEVMO with sensitive CYP2C8 substrates. If coadministration cannot be avoided, modify the substrate dosage as recommended in its product labeling.
Effect of selpercatinib on sensitive CYP3A4 substrates			
Sensitive CYP3A4 substrates, including but not limited to midazolam, alfentanil, avanafil, buspirone, darifenacin, darunavir, everolimus, lomitapide, ibrutinib, lovastatin, naloxegol, simvastatin, tipranavir, triazolam, vardenafil	CT, T	Coadministration of multiple doses of RETEVMO (160 mg BID) with midazolam (2 mg QD) increased the midazolam $AUC_{0\text{-}INF}$ by 54% and C_{max} by 39%.	Avoid coadministration of RETEVMO with sensitive CYP3A4 substrates. If coadministration cannot be avoided, modify the substrate dosage as recommended in its product labeling.
Effect of selpercatinib on transporters			
MATE1 substrates, including but not limited to creatinine	T	Selpercatinib inhibits the renal transporter multidrug and toxin extrusion protein 1 (MATE1).	Selpercatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine via inhibition of MATE1. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed, such as cystatin C, BUN, or calculated GFR. No clinically significant differences in glucose levels were observed when metformin (MATE1 substrate) was coadministered with selpercatinib.

Legend: CT=Clinical Trial; T=Theoretical.

P-glycoprotein (P-gp) Inhibitors: Coadministration of single dose of RETEVMO (160 mg QD) with single dose of rifampin (P-gp inhibitor, 600 mg QD) increased the selpercatinib AUC0-INF by 6% and Cmax by 19% and is not clinically significant.

P-gp Substrates: Coadministration of RETEVMO with dabigatran (P-gp substrate) increased the dabigatran $AUC_{0\text{-}INF}$ by 38% and C_{max} by 43%.

Avoid coadministration of RETEVMO with P-gp substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for P-gp substrates provided in their approved product labeling.

In vitro drug interactions: In vitro, selpercatinib does not inhibit or induce CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations. Selpercatinib is not a substrate for transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K.

Other QTc Interval-Prolonging Drugs

The concomitant administration of RETEVMO with other drugs known to prolong the QTc interval or induce torsade de pointes should be avoided. Current information sources should be consulted for lists of drugs that prolong the QTc interval.

When it is not feasible to avoid concomitant use of drugs known to prolong the QTc interval, obtain ECGs and serum electrolytes measurements prior to and after initiation of any drug known to prolong the QTc interval. Perform more frequent ECG monitoring as clinically indicated during treatment.

Drugs that Affect Electrolytes

Use of RETEVMO with drugs that can decrease electrolyte levels should be avoided to the extent possible as this may increase the risk of QTc interval prolongation. Such drugs include, but are not limited to, the following: loop diuretics, thiazide and related diuretics, laxatives, enemas, amphotericin B, high-dose corticosteroids, and proton pump inhibitors.

Drugs that Reduce Heart Rate

Avoid using RETEVMO concomitantly with drugs that reduce heart rate, including, but not limited to, beta-blockers, digitalis glycosides, non-dihydropyridine calcium channel blockers, cholinesterase inhibitors, alpha2-adrenoceptor agonists, I_f inhibitors, and sphingosine-1 phosphate receptor modulators.

9.5 Drug-Food Interactions

RETEVMO may be administered with or without food unless coadministered with a proton pump inhibitor (see 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics). Grapefruit can inhibit cytochrome P450 CYP3A enzymes and potential drug interactions of grapefruit and grapefruit containing products with RETEVMO cannot be ruled out.

9.6 Drug-Herb Interactions

St. John's Wort (hypericum perforatum) is a strong CYP3A inducer. Co-administration of St. John's Wort with RETEVMO should be avoided.

9.7 Drug–Laboratory Test Interactions

RETEVMO may increase serum creatinine by decreasing renal tubular secretion of creatinine via inhibition of MATE1, without affecting glomerular function. In healthy subjects administered RETEVMO 160 mg orally twice daily, serum creatinine increased 18% after 10 days. If persistent elevations in serum creatinine are observed, alternative markers of renal function should be considered, such as cystatin C, blood urea nitrogen (BUN), or calculated glomerular filtration rate (GFR).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Selpercatinib is an orally available, small molecule kinase inhibitor. In enzyme assays, selpercatinib inhibited the “rearranged during transfection” (RET) receptor tyrosine kinase, VEGFR3 (FLT4) and VEGFR1 (FLT1) kinases with IC_{50} values ranging from 0.92 nM to 67.6 nM. Selpercatinib also inhibited FGFR1, 2 and 3 at higher concentrations. In cellular assays, selpercatinib inhibited RET at an IC_{50} approximately 60-fold lower than the IC_{50} for FGFR1 and 2 and approximately 8-fold lower than the IC_{50} for VEGFR3. In radioligand binding assays at a concentration of 1μM, selpercatinib inhibited the 5-HT transporter (70.2%) and the α2C receptor (51.7%).

Chromosomal rearrangements involving in-frame fusions of *RET* with various partners can result in constitutively activated chimeric RET fusion proteins that can act as oncogenic drivers, promoting cell proliferation and survival in tumor cell lines. Point mutations in *RET* can also result in constitutively activated RET proteins that can promote cell growth and survival in tumor cell lines.

In RET enzyme assays, selpercatinib inhibits the kinase activity of wild type RET and multiple mutated forms of RET *(*RET-V804L, RET-V804M, RET-A883F, RET-S904F, and RET-M918T) with IC_{50} values of 0.20 nM to 2.21 nM.

Selpercatinib demonstrated in vitro inhibition of human cancer cell lines derived from multiple tumor types harboring *RET* fusion genes and *RET* mutations with EC_{50} values equal to 10 nM or less. In in vivo mouse studies, selpercatinib demonstrated inhibition of tumor growth in *RET* fusion and *RET* mutant cancer cell lines, patient-derived *RET* fusion xenograft models, and a patient-derived *RET* fusion xenograft model harboring a *RET* V804M mutation. Selpercatinib also exhibited intracranial anti-tumor activity of patient-derived *RET* fusion xenograft tumors implanted directly into the brain of mice.

10.2 Pharmacodynamics

Cardiac Electrophysiology

In a randomised, double-blind, placebo- and positive controlled, 4-way crossover ECG assessment study in 32 healthy subjects, selpercatinib at single supratherapeutic doses of 320 mg and 640 mg was associated with a concentration-dependent prolongation of the QTcF interval ($QTcF=QT/RR^{0.33}$). The maximum difference from placebo in mean change from baseline QTcF was 8.1 ms (90% CI 4.3, 11.9) at 12 h post-dosing in the 320 mg arm and 9.7 ms (90% CI 7.0, 12.5) at 2.5 h post-dosing in the 640 mg treatment arm. The mean Cmax values were 2024 ng/mL and 2356 ng/mL after the single 320 mg and 640 mg doses, respectively.

According to a pharmacokinetic-pharmacodynamic model, the predicted magnitude of QTcF prolongation is 10.7 ms (90% CI 9.3, 12.2) at the mean steady-state Cmax value of

2980 ng/mL reported for the 160 mg twice-daily therapeutic dose administered for 8 days to cancer patients and 16.8 ms (90% CI 14.4, 19.2) at the mean steady-state Cmax value of 4574 ng/mL reported for the 160 mg twice-daily dose administered for 9 days to healthy subjects.

On day 8 of treatment in cancer patients (N=564) initiated at the 160 mg twice-daily dose of RETEVMO in the uncontrolled LIBRETTO-001 trial, the mean change from baseline QTcF was 22.4 ms (95% CI 20.6, 24.2) at 2 h post-dosing.

10.3 Pharmacokinetics

The pharmacokinetics of selpercatinib were evaluated in patients with locally advanced or metastatic solid tumors administered 160 mg twice daily unless otherwise specified. Steady-state selpercatinib AUC and C_{max} increased in a slightly greater than dose proportional manner over the dose range of 20 mg once daily to 240 mg twice daily (0.06 to 1.5 times the maximum recommended total daily dosage).

Steady-state was reached by approximately 7 days and the median accumulation ratio after administration of 160 mg twice daily was 3.4-fold for AUC and 2.66 for C_{max}. Mean steady-state selpercatinib C_{max} was 2,980 ng/mL, AUC_{0-24h} was 51,600 ng*h/mL, t½ was 24.5 hours and CLss/F was 6 L/hr after administration of selpercatinib 160 mg BID in cancer patients (Table 9). The pharmacokinetics of selpercatinib were comparable between cancer patients and healthy volunteers.

Table 9 - Summary of Selpercatinib Pharmacokinetic Parameters in Cancer Patients Administered 160 mg BID at Steady State

	C_{max} (CV%)	T_{max} (CV%)	AUC_{0-24h} (CV%)	t½ (CV%)	CLss/F (CV%)	Vss/F (CV%)
Steady state mean	2980 ng/mL (53.1%)	2 h (8.1%)	51600 ng*h/mL (57.9%)	24.5 h (68.3%)	6.0 L/h (57.9%)	191 L (69%)

CV% = coefficient of variation.

Absorption

After an oral dose of 160 mg in adult patients and in healthy subjects, selpercatinib was rapidly absorbed, with T_{max} of approximately 2 hours. Geometric mean absolute oral bioavailability in healthy subjects was 73.2%.

Effect of food: Compared to selpercatinib AUC_T, C_{max} and T_{max} in the fasted state, selpercatinib AUC_T was increased by 9% and C_{max} was reduced by 14% and T_{max} was delayed from 1.5 hours to 4.0 hours after oral administration of a single 160 mg dose (2 x 80 mg) to healthy subjects taken with a high-fat, high calorie meal.

Distribution

The apparent volume of distribution (Vss/F) of selpercatinib is 191 L. Protein binding of selpercatinib is 97% in vitro and is independent of concentration. The blood- to-plasma concentration ratio is 0.7.

Metabolism

Selpercatinib is metabolized predominantly by CYP3A4. Following oral administration of a single [^{14}C] radiolabeled 160 mg dose of selpercatinib to healthy subjects, unchanged selpercatinib constituted 86% of the radioactive drug components in plasma.

Elimination

Following oral administration of a single [^{14}C] radiolabeled 160 mg dose of selpercatinib to healthy subjects, 69% of the administered radioactivity was recovered in feces and 24% was recovered in urine.

Special Populations and Conditions

- **Pediatrics** Very limited pharmacokinetics data are available for patients 15 to 17 years of age. There are no data on the pharmacokinetics of selpercatinib in pediatric patients younger than 15 years of age.
- **Geriatrics** Based on a population pharmacokinetic analysis of the LIBRETTO-001 study, the pharmacokinetics of selpercatinib in patients ≥65 years of age were comparable to patients between 18 years to 65 years.
- **Patients with body weight <50 kg** The apparent volume of distribution and clearance of selpercatinib increase with increasing body weight (27 kg to 177 kg). In subjects <50 kg, the AUC_{0-12} and the C_{max} of selpercatinib were respectively approximately 50% and 70% higher than in subjects with bodyweights 70-80 kg. Dosing adjustment is required in subjects < 50 kg (see 4 DOSAGE AND ADMINISTRATION).
- **Hepatic insufficiency** In subjects with mild or severe hepatic impairment according to the Child-Pugh classification, unbound AUC_{inf} of selpercatinib increased approximately by 33%, and 228.4% respectively and unbound C_{max} increased by approximately 78.2%, and 131.6% respectively, compared to subjects with normal hepatic function. No changes in unbound AUC_{inf} and unbound C_{max} were observed in subjects with moderate hepatic impairment. No dose adjustment is recommended for patients with mild or moderate hepatic impairment. Reduce the dose of RETEVMO in patients with severe hepatic impairment to 80 mg twice daily (see 4 DOSAGE AND ADMINISTRATION and 7.1 Special Populations).
- **Renal insufficiency** In subjects with mild (eGFR: 60 – <90 ml/min/1.73m^2), moderate (eGFR: 30 – 59 ml/min/1.73m^2), or severe (eGFR: <30 ml/min/1.73m^2) renal impairment administered selpercatinib 160 mg QD, AUC_{inf} of selpercatinib increased by approximately 21.7%, 50.1%, and 12.5% respectively in subjects with mild, moderate or severe renal impairment compared to subjects with normal renal function. C_{max} of selpercatinib increased by 69%, 29.5% and decreased by 14.7% in subjects with mild, moderate or severe renal impairment compared to subjects with normal renal function. No dosage adjustment is necessary in patients with mild, moderate or severe renal impairment.

  The effect of end-stage renal disease on the pharmacokinetics and safety of selpercatinib have not been evaluated. The use of selpercatinib in patients with end-stage renal disease is not recommended.
- **Ethnic Origin, sex** Based on a population pharmacokinetic analysis, ethnic origin and sex had no clinically meaningful effect on the pharmacokinetics of selpercatinib.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15° to 30°C).

12 SPECIAL HANDLING INSTRUCTIONS

This information is not available for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

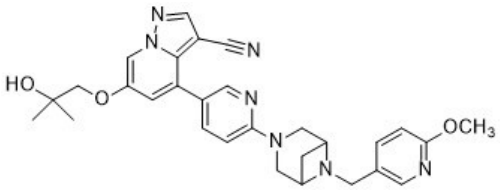
Drug Substance

Proper/Common name: selpercatinib

Chemical name: 6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile]

Molecular formula and molecular mass: $C_{29}H_{31}N_7O_3$; formula weight of 525.6 g/mol

Structural formula:



Physicochemical properties: Selpercatinib is an anhydrous, crystalline (Form A), white to practically white to light yellow powder. The aqueous solubility of selpercatinib is pH dependent, from sparingly soluble at low pH (≥10 mg/mL at pH 1.3) to practically insoluble at neutral pH (0.002 mg/mL at pH 7.5).

14. CLINICAL TRIALS

14.1 Clinical Trials by Indication

Metastatic *RET* Fusion-Positive Non-Small Cell Lung Cancer

Table 10 - Summary of Patient Demographics for Clinical Trials in *RET* Fusion-Positive NSCLC

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex, n (%)
LIBRETTO-001	Open label, multicenter, multi-cohort, Phase 1/2 study	Patients received RETEVMO 160 mg orally twice daily until unacceptable toxicity or disease progression	Patients previously treated with platinum-based chemotherapy (105)	61 (23-81) years	Male: 43 (41) Female: 62 (59)
			Treatment-naïve patients (39)	61 (23-86) years	Male: 17(44) Female: 22 (56)

The efficacy of RETEVMO in patients with advanced *RET* fusion-positive NSCLC was evaluated in a phase 1/2, multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001; see Table 10). Identification of a *RET* gene alteration was prospectively determined in local laboratories using next generation sequencing (NGS), polymerase chain reaction (PCR), or fluorescence *in situ* hybridization (FISH). Among *RET* fusion-positive NSCLC patients, the most common fusion partner was KIF5B, followed by CCDC6 and then NCOA4. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as determined by an independent review committee (IRC) according to RECIST v1.1.

In patients with *RET* fusion-positive NSCLC who were previously treated with platinum-based chemotherapy, 52% were White, 38% were Asian, 4.8% were Black, and 3.8% were Hispanic/Latino. ECOG performance status was 0-1 (98%) or 2 (2%), and 98% of patients had metastatic disease. Patients received a median of 3 prior systemic therapies (range: 1-15), and 58 patients had prior anti-PD-1/PD-L1 therapy. At initial diagnosis, the majority of patients (87.6%) were diagnosed with nonsquamous NSCLC; one patient (1%) had squamous cell NSCLC; and the histology was unknown in 11.4% of patients. *RET* fusions were detected in 89.6% of patients using NGS (81.0% tumor samples, 8.6% blood or plasma samples); 8.6% using FISH; and 1.9% using PCR.

In patients with *RET* fusion-positive NSCLC who were treatment-naïve, 72% were White, 18% were Asian, and 8% were Black. ECOG performance status was 0-1 in all patients (100%) and all patients had metastatic disease. *RET* fusions were detected in 92.3% of patients using NGS (64.1% tumor samples, 28.2% blood or plasma samples); and 7.7% using FISH.

Efficacy results for patients with *RET* fusion-positive NSCLC previously treated with platinum chemotherapy are summarized in Table 11. A waterfall plot illustrating the best change in tumor size per RECIST v1.1 and based on independent review committee assessment is shown in Figure 1.

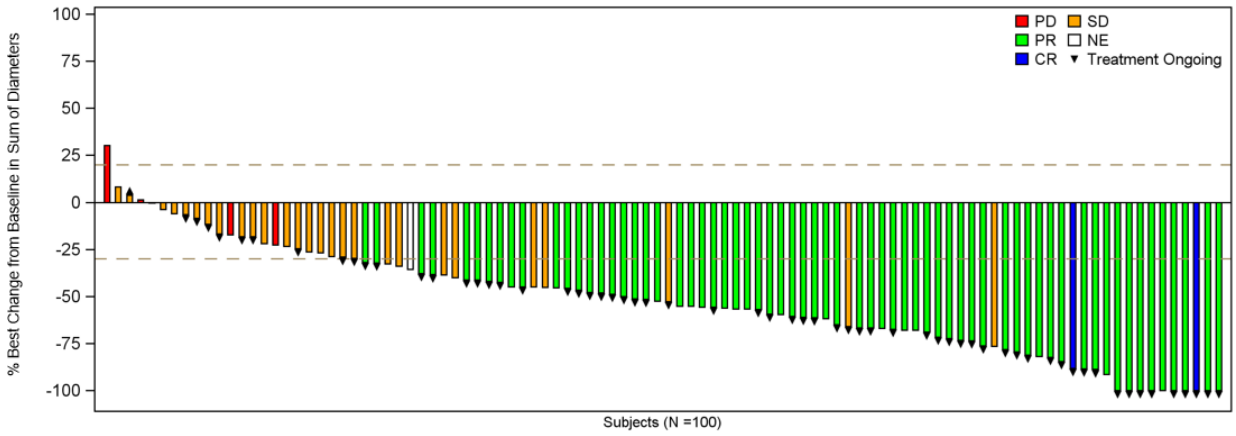
Table 11 - Efficacy Results in Patients with Metastatic *RET* Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy - LIBRETTO-001

	RETEVMO (n=105)
Overall Response Rate[a] (95% CI)	64% (54%, 73%)
Complete response	1.9%
Partial response	62%
Duration of Response	
Median in months (95% CI)	17.5 (12, NE)

[a] Confirmed overall response rate assessed by independent review committee.

CI=confidence interval; NE=not estimable.

Figure 1 - Waterfall Plot of Best Change in Tumor Burden in Patients with Metastatic *RET* Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy – LIBRETTO-001



Based on independent review committee assessment

PD=progressive disease; SD=stable disease; PR=partial response; NE=not estimable; CR=complete response.

Note: Five patients not shown due to 2 patients having non-target lesions only, and 3 patients with no post-baseline target lesion measurement.

The efficacy of RETEVMO in patients with *RET* fusion-positive NSCLC of squamous histology has not been fully evaluated due to limited clinical data.

An exploratory subgroup analysis showed that, among the 58 patients who received an anti-PD-1 or anti-PD-L1 therapy, either sequentially or concurrently with platinum-based chemotherapy, the ORR was 66% (95% CI: 52%, 78%) and the median DOR was not reached (95% CI: 12.0, not estimable).

Among the 105 patients with *RET* fusion-positive NSCLC, 11 had measurable central nervous system metastases at baseline as assessed by IRC. No patient received radiation therapy to the brain within 2 months prior to study entry. Responses in intracranial lesions were observed in 10 of these 11 patients; the median duration of response for patients with measurable CNS disease at baseline was 10.1 months (95% CI: 6.7, NE).

Efficacy results for patients with treatment naïve *RET* fusion-positive NSCLC are summarized in Table 12. A waterfall plot illustrating the best change in tumor size per RECIST v1.1 and based on independent review committee assessment is shown in Figure 2.

Table 12 - Efficacy Results in Patients with Treatment-Naïve Metastatic *RET* Fusion-Positive NSCLC - LIBRETTO-001

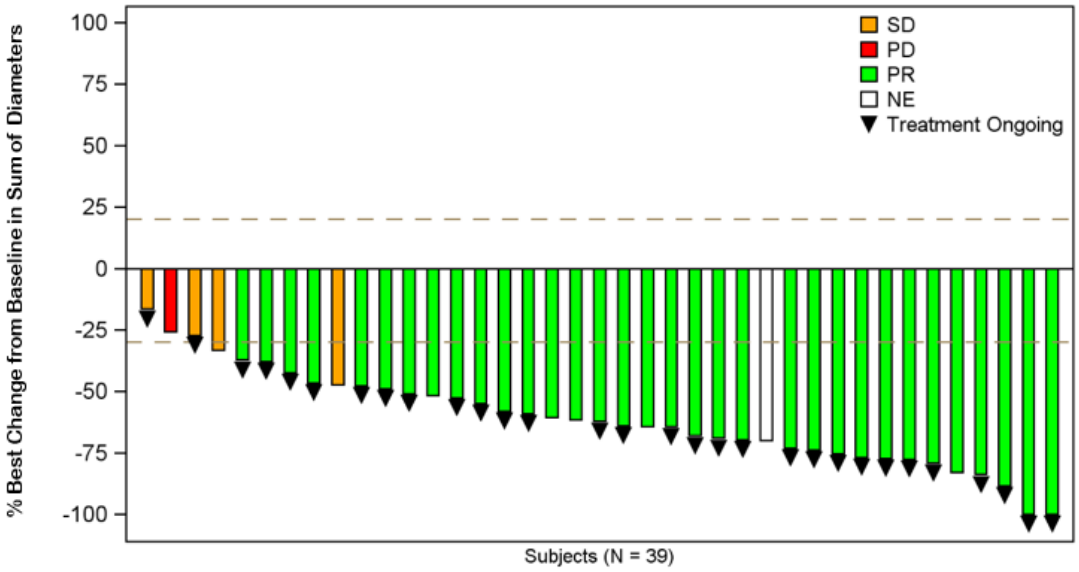
	RETEVMO (n=39)
Overall Response Rate[a] (95% CI)	85% (70%, 94%)
Complete response	0
Partial response	85%

[a] Confirmed overall response rate assessed by independent review committee.

CI=confidence interval.

The median follow-up of patients with treatment-naïve NSCLC was not long enough for estimating the duration of response.

Figure 2 - Waterfall Plot of Best Change in Tumor Burden in Patients with Treatment-Naïve *RET* Fusion-Positive NSCLC - LIBRETTO-001



Based on independent review committee assessment

PD=progressive disease; SD=stable disease; PR=partial response; NE=not estimable.

RET-Mutant Medullary Thyroid Cancer

Table 13 - Summary of Patient Demographics for Clinical Trials in *RET*-Mutant Medullary Thyroid Cancer

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex, n (%)
LIBRETTO-001	Open label, multicenter, multi-cohort, Phase 1/2 study	Patients received RETEVMO 160 mg orally twice daily until unacceptable toxicity or disease progression	Patients previously treated with vandetanib or cabozantinib (or both) (55)	57 (17-84) years	Male: 36 (66) Female: 19 (34)
			Vandetanib and cabozantinib treatment-naïve patients (88)	58 (15-82) years	Male: 58 (66) Female: 30 (34)

The efficacy of RETEVMO in patients with *RET*-mutant MTC was evaluated in a phase 1/2, multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001; see Table 13). Identification of a *RET* gene alteration was prospectively determined in local laboratories using next generation sequencing (NGS), polymerase chain reaction (PCR), or fluorescence *in situ* hybridization (FISH). Among *RET*-mutant MTC patients, the most common mutation was M918T, followed by extracellular cysteine mutation. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as determined by an independent review committee (IRC) according to RECIST v1.1.

In patients with *RET*-mutant MTC who were previously treated with vandetanib (76.4% of patients) or cabozantinib (67.3% of patients), 89% were White, 7% were Hispanic/Latino, and 1.8% were Black. One pediatric patient was included (17 years of age). ECOG performance status was 0-1 (95%) or 2 (5%), and 98% of patients had metastatic disease. Patients received a median of 2 prior systemic therapies (range: 1-8). *RET* mutation status was detected in 82% of patients using NGS (78% tumor samples; 4% blood or plasma), 16% using PCR, and 2% using an unknown test. The protocol excluded patients with synonymous, frameshift, or nonsense *RET* mutations.

In patients with *RET*-mutant MTC who were vandetanib and cabozantinib treatment-naïve, 86% were White, 4.5% were Asian, and 2.3% were Hispanic/Latino. Two pediatric patients were included (ages 15 years and 16 years). ECOG performance status was 0-1 (97%) or 2 (3%). All patients (100%) had metastatic disease, and 18% had received 1 or 2 prior systemic therapies (including 8% kinase inhibitors, 3.4% chemotherapy, 2.3% anti-PD1/PD-L1 therapy, and 1.1% radioactive iodine). *RET* mutation status was detected in 77.3% of patients using NGS (75% tumor samples, 2.3% blood samples); 18.2% using PCR; and 4.5% using an unknown test.

Efficacy results for patients with metastatic *RET*-mutant MTC previously treated with vandetanib or cabozantinib are summarized in Table 14. A waterfall plot illustrating the best change in tumor size per RECIST v1.1 based on independent review committee assessment is shown in Figure 3.

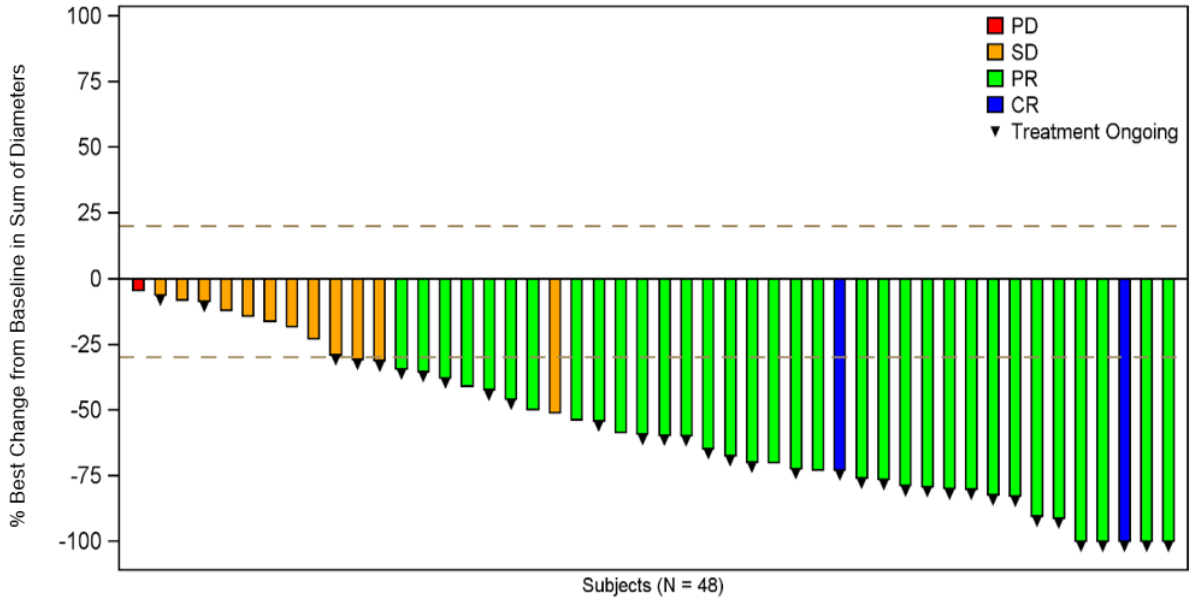
Table 14- Efficacy Results in Patients with Metastatic *RET*-Mutant MTC Previously Treated with Vandetanib or Cabozantinib - LIBRETTO-001

	RETEVMO (n=55)
Overall Response Rate[a] (95% CI)	69% (55%, 81%)
Complete response	9%
Partial response	60%

[a] Confirmed overall response rate assessed by independent review committee.

CI=confidence interval.

Figure 3 - Waterfall Plot of Best Change in Tumor Burden in Patients with Metastatic *RET*-Mutant MTC Previously Treated with Vandetanib or Cabozantinib - LIBRETTO-001



Based on independent review committee assessment

PD=progressive disease; SD=stable disease; PR=partial response; CR=complete response.

Note: Seven patients are not included because 5 patients have non-target lesion only, and 2 patients discontinued study early with no post-baseline target lesion measurement.

Efficacy results for patients with vandetanib and cabozantinib-naïve metastatic *RET*-mutant MTC are summarized in Table 15. A waterfall plot illustrating the best change in tumor size per RECIST v1.1 based on independent review committee assessment is shown in Figure 4.

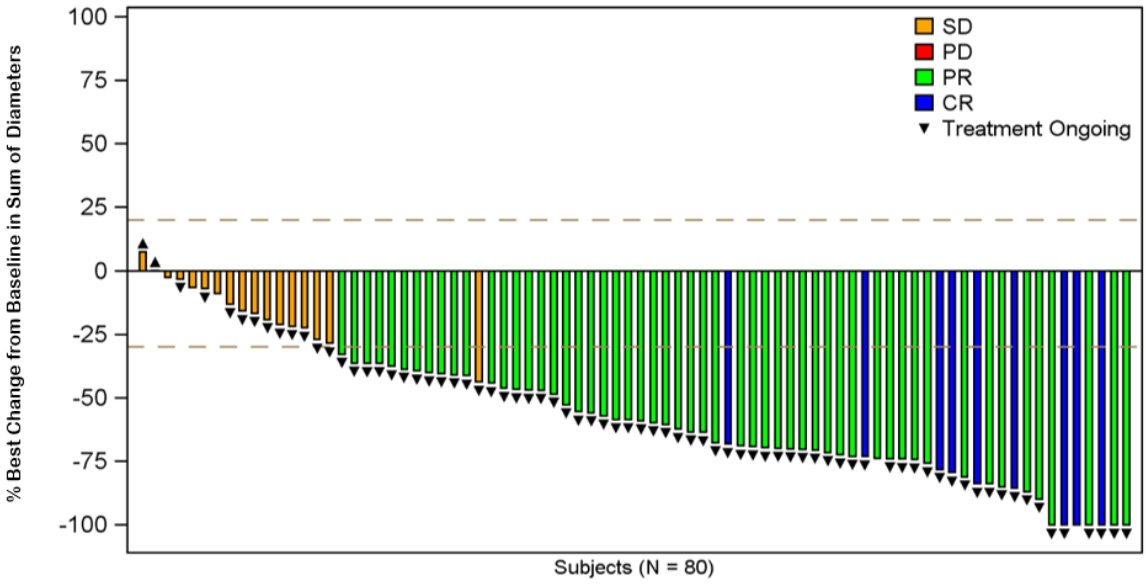
Table 15 - Efficacy Results in Patients with Vandetanib and Cabozantinib-Naïve Metastatic *RET*-Mutant MTC - LIBRETTO-001

	RETEVMO (n=88)
Overall Response Rate[a] (95% CI)	73% (62%, 82%)
Complete response	11%
Partial response	61%

[a] Confirmed overall response rate assessed by independent review committee.

CI=confidence interval.

Figure 4 - Waterfall Plot of Best Change in Tumor Burden in Patients with Vandetanib and Cabozantinib-Naïve Metastatic *RET*-Mutant MTC Patients - LIBRETTO-001



Based on independent review committee assessment

PD=progressive disease; SD=stable disease; PR=partial response; CR=complete response.

RET Fusion-Positive Thyroid Cancer

Table 16 - Summary of Patient Demographics for Clinical Trials in *RET* Fusion-Positive Thyroid Cancer

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex, n (%)
LIBRETTO-001	Open label, multicenter, multi-cohort, Phase 1/2 study	Patients received RETEVMO 160 mg orally twice daily until unacceptable toxicity or disease progression	Patients were radioactive iodine (RAI)-refractory (if RAI was an appropriate treatment option) (27)	54 (20-88) years	Male: 14 (52) Female: 13 (48)

The efficacy of RETEVMO in patients with *RET* fusion-positive thyroid cancer was evaluated in a phase 1/2, multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001; see Table 16). Identification of a *RET* gene alteration was prospectively determined in local laboratories using next generation sequencing (NGS), polymerase chain reaction (PCR), or fluorescence *in situ* hybridization (FISH). For patients with *RET* fusion-positive thyroid cancers, CCDC6 was the most common fusion partner. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as determined by an independent review committee (IRC) according to RECIST v1.1.

In patients with *RET* fusion-positive thyroid cancer, 74% were White, 11% were Hispanic/Latino, 7.4% were Asian, and 3.7% were Black. ECOG performance status was 0-1 (89%) or 2 (11%). All (100%) patients had metastatic disease with primary tumor histologies including papillary thyroid cancer (21 patients; 78%), poorly differentiated thyroid cancer (3 patients), anaplastic thyroid cancer (2 patients), or Hurthle cell thyroid cancer (1 patient). Patients were radioactive iodine (RAI)–refractory (if RAI was an appropriate treatment option) and had received a median of 3 prior therapies (range: 1-7). *RET* fusion-positive status was detected in 93% of patients using NGS tumor samples and in 7% using blood samples. Efficacy was evaluated in a cohort of patients (n=19) who were RAI-refractory and who had received sorafenib, lenvatinib, or both.

Efficacy results for patients with metastatic *RET* fusion-positive thyroid cancer who received prior systemic therapy are summarized in Table 17.

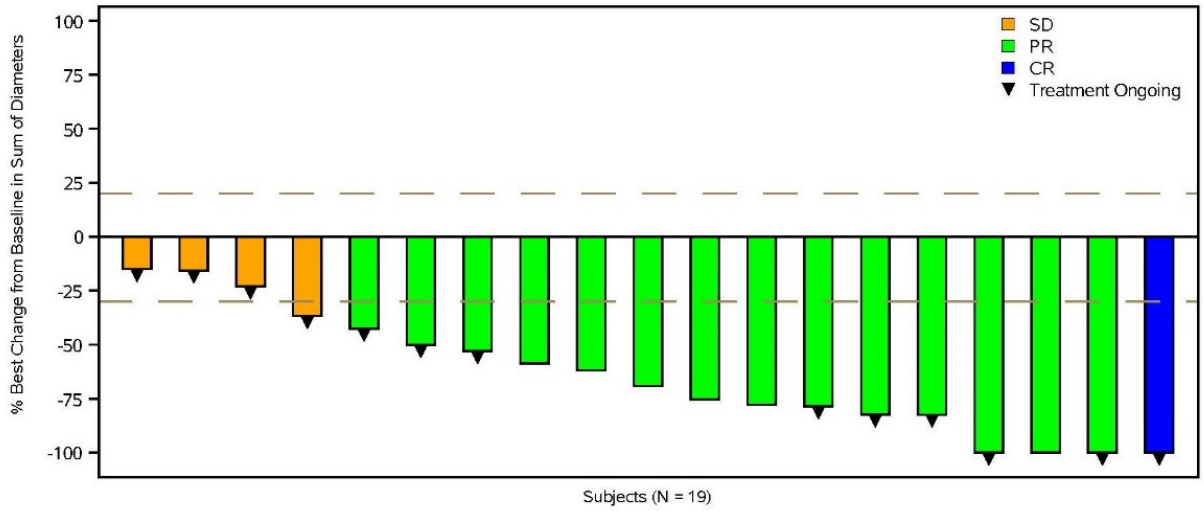
Table 17 - Efficacy Results in Patients with Metastatic *RET* Fusion-Positive Thyroid Cancer who Received Prior Systemic Therapy - LIBRETTO-001

	RETEVMO (n=19)
Overall Response Rate[a] (95% CI)	79% (54%, 94%)
Complete response	5.3%
Partial response	74%
Duration of Response	
Median in months (95% CI)	18.4 (7.6, NE)

[a] Confirmed overall response rate assessed by independent review committee.

CI=confidence interval; NE=not estimable.

Figure 5 - Waterfall Plot of Best Change in Tumor Burden in Patients with Metastatic *RET* Fusion-Positive Thyroid Cancer who received prior systemic therapy - LIBRETTO-001



Based on independent review committee assessment

PD=progressive disease; SD=stable disease; PR=partial response; CR=complete response.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Repeat-dose studies were conducted in rats and minipigs to characterize toxicity. Target organs of toxicity common to the rat and minipig were hematopoietic system, lymphoid tissues, tongue, pancreas, epiphyseal growth plate, and male reproductive tissues. In general, toxicities in these organs were reversible; the exception was the testicular toxicity. Reversible toxicity was observed in the ovaries and gastrointestinal tract in minipigs only; at

high doses, gastrointestinal toxicity caused morbidity at exposures in minipigs that were generally lower than exposures determined in humans at the recommended dose. In one minipig study, females exhibited a slight, reversible increase in QTc prolongation of approximately 12% compared to controls and 7% compared to pre-dose values. Target organs of toxicity observed only in rats were incisor tooth, liver, vagina, lungs, Brunner's gland, and multi-tissue mineralization associated with hyperphosphatemia. These toxicities only occurring in these organs in rats were reversible.

In a 4-week general toxicology study, adolescent rats showed signs of physeal hypertrophy and tooth dysplasia at doses resulting in exposures ≥ approximately 3 times the human exposure at the 160 mg twice daily clinical dose. In a 13-week general toxicity study, adolescent minipigs showed signs of minimal to marked increases in physeal thickness at the 15 mg/kg high dose level (approximately 0.3 times the human exposure at the 160 mg twice daily clinical dose). Rats in both the 4- and 13-week toxicology studies had malocclusion and tooth discoloration at the high dose levels (≥1.5 times the human exposure at the 160 mg twice daily clinical dose) that persisted during the recovery period.

Genotoxicity and Carcinogenicity: Carcinogenicity studies have not been conducted with selpercatinib.

Selpercatinib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assays, with or without metabolic activation, or clastogenic in the in vitro micronucleus assay in human peripheral lymphocytes, with or without metabolic activation. Selpercatinib was positive in the in vivo micronucleus assay in rats at concentrations >7 times the C_{max} at the human dose of 160 mg twice daily.

Reproductive and Development Toxicology: In general toxicology studies, male rats and minipigs exhibited testicular degeneration that was associated with luminal cell debris and/or reduced luminal sperm in the epididymis at selpercatinib exposures approximately 0.4 (rat) and 0.1 (minipig) times the clinical exposure by AUC at the recommended human dose of 160 mg twice daily. In a dedicated fertility study in male rats, administration of selpercatinib at doses up to 30 mg/kg/day (approximately twice the clinical exposure by AUC at the 160 twice-daily dose) for 28 days prior to cohabitation with untreated females did not affect mating or have clear effects on fertility. Males did, however, display a dose-dependent increase in testicular germ cell depletion and spermatid retention at doses ≥3 mg/kg (~0.2 times the clinical exposure by AUC at the 160 twice-daily dose) accompanied by altered sperm morphology at 30 mg/kg.

In a dedicated fertility study in female rats treated with selpercatinib for 15 days before mating to Gestational Day 7, there were decreases in the number of estrous cycles at a dose of 75 mg/kg (approximately equal to the human exposure by AUC at the 160 mg twice-daily clinical dose). Although selpercatinib did not have clear effects on mating performance or ability to become pregnant at any dose level, half of females at the 75 mg/kg dose level had 100% nonviable embryos. At the same dose level in females with some viable embryos, there were increases in post-implantation loss.

Selpercatinib administration to pregnant rats during the period of organogenesis at oral doses ≥100 mg/kg [approximately 3.6 times the human exposure based on the area under the curve (AUC) at the clinical dose of 160 mg twice daily] resulted in 100% post-implantation loss. At the dose of 50 mg/kg [approximately equal to the human exposure (AUC) at the clinical dose of 160 mg twice daily], 6 of 8 females had 100% early resorptions; the remaining 2 females had high levels of early resorptions with only 3 viable fetuses across the 2 litters. All viable fetuses had decreased fetal body weight and malformations (2 with short tail and one with small snout and localized edema of the neck and thorax).

In the general toxicology study in minipigs, there were findings of decreased or absent corpora lutea at a selpercatinib dose of 15 mg/kg (approximately 0.3 times the human exposure by AUC at the 160 mg twice-daily clinical dose). Corpora luteal cysts were present in the minipig at selpercatinib doses ≥2 mg/kg (approximately 0.07 times the human exposure by AUC at the 160 mg twice-daily clinical dose).

Juvenile Toxicity: In a study in juvenile rats, epiphyseal growth plate changes similar to those in adolescent rats were observed. These changes were associated with decreased femur length and reductions in bone mineral density, and were not reversible.

Large intestinal enteropathy was characterized by increased basophilia and occasional vacuolation of the crypt epithelium.

In juvenile male rats administered selpercatinib as juveniles and mated as adolescents with untreated female rats, the following effects on reproductive performance were observed: lower male fertility and copulation indices, increased pre-implantation loss, increased post-implantation loss, and lower mean number and proportion of viable embryos.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrRETEVMO™

Selpercatinib capsules

Read this carefully before you start taking RETEVMO and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about RETEVMO.

Serious Warnings and Precautions

- Only a doctor who has experience treating cancer should treat you with this drug.
- RETEVMO can harm your unborn baby.
- RETEVMO can cause serious side effects including:
    - **Hemorrhage** (severe bleeding; blood loss): Bleeding can occur with RETEVMO treatment and can be serious. It may even cause death. If you experience bleeding, your doctor may stop your treatment.
    - **Liver problems:** Liver problems and increased liver enzymes are very common with RETEVMO and may sometimes be serious. Your healthcare professional will run blood tests to check your liver before and during treatment.
    - **Allergic reactions:** RETEVMO may cause a fever, rash, muscle or joint pain. This is common in the first month of treatment. If you experience an allergic reaction, your doctor may prescribe medicine to treat your reaction.
    - **Hypertension** (high blood pressure): High blood pressure is very common with RETEVMO and may sometimes be serious. Your blood pressure should be well controlled before you start taking RETEVMO. Your healthcare professional should check your blood pressure regularly when you take RETEVMO. If blood pressure becomes a problem, your doctor may prescribe medicine to treat your high blood pressure.
    - **QT prolongation** (a heart rhythm condition): Changes to your heart rhythm can occur with RETEVMO treatment and can be serious. Your healthcare professional will check that your heart is working properly before and during your treatment.

See the Serious side effects and what to do about them table, below, for more information on these serious side effects.

What is RETEVMO used for?

See the following boxed text:

For the following indications, RETEVMO has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

RETEVMO is used to treat certain cancers caused by abnormal *RET* genes in:

- adults with a type of lung cancer called non-small cell lung cancer (NSCLC). It is used when your cancer has spread to other parts of your body.
- adults and children 12 to 17 years old with medullary thyroid cancer. It is used when:
    - your cancer is advanced or has spread to other parts of your body, and
    - your cancer cannot be removed using surgery
- adults with differentiated thyroid cancer. It is used when:
    - your cancer is advanced or has spread to other parts of your body,
    - your cancer cannot be removed using surgery,
    - radioactive iodine therapy did not work, is no longer working or is not appropriate, and
    - you have tried treatment with sorafenib and/or lenvatinib

Your healthcare professional will perform a test to make sure that RETEVMO is right for you.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does RETEVMO work?

RETEVMO works by blocking the action of RET protein kinase. Specific RET altered proteins can lead to uncontrolled cell growth and cancer. RETEVMO stops specific RET altered proteins from working. RETEVMO may slow or stop the cancer from growing. It may also help to shrink the cancer.

What are the ingredients in RETEVMO?

Medicinal ingredients: selpercatinib

Non-medicinal ingredients: Black iron oxide, colloidal silicon dioxide, FD & C Blue No. 1 (80 mg capsule only), gelatin, microcrystalline cellulose, pharmaceutical grade printing ink, titanium dioxide

RETEVMO comes in the following dosage forms:

Capsule: 40 mg and 80 mg

Do not use RETEVMO if:

- You are allergic to selpercatinib or any of the other ingredients in this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RETEVMO. Talk about any health conditions or problems you may have, including if you have:

- heart problems or have a family history of heart problems, including a condition known as QT prolongation. QT prolongation happens when there are changes in the electrical activity of the heart. This can cause heart rhythm problems.
- high blood pressure
- liver problems
- kidney problems
- diabetes
- a recent history of significant bleeding
- a history of stroke or brain injury
- a history of anorexia or other eating disorder
- persistent vomiting
- been told that you have an imbalance of electrolytes in your blood, such as potassium, magnesium or calcium
- a condition called “autonomic neuropathy” that causes problems with blood pressure, heart rate, sweating, bowel and bladder control and digestion

Other warnings you should know about:

Risk of wound healing problems: Wounds may not heal properly during treatment with RETEVMO. Tell your healthcare professional if you plan to have any surgery before or during treatment with RETEVMO.

- You should stop taking RETEVMO at least 7 days before planned surgery.
- Your healthcare professional should tell you when you may start taking RETEVMO again after surgery.

Tumor lysis syndrome: RETEVMO can cause a serious side effect known as Tumor lysis syndrome (TLS). TLS is caused by a sudden, rapid death or breakdown of cancer cells due to treatment. TLS is a condition that can cause kidney failure and abnormal heart rhythm. You may be at risk of TLS if you have:

- Tumors that are growing quickly,
- Many or large tumours,
- Problems with your kidneys or
- You do not have enough water or fluids in your body.

Your healthcare professional will check you for signs and symptoms of TLS. Drink plenty of water when taking RETEVMO to stay well hydrated.

Pregnancy and breastfeeding:

Female patients:

- If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your healthcare professional.
- You should not take RETEVMO if you are pregnant. It can harm your unborn baby.
- If you are able to become pregnant:
    - Your healthcare professional will do a pregnancy test before you start RETEVMO. This test must show that you are not pregnant.
    - Avoid becoming pregnant while you are taking RETEVMO. Use highly effective birth control during treatment and for at least 2 weeks after your last dose. Talk to your healthcare professional about birth control methods that may be right for you during this time.
    - Tell your healthcare professional right away if you become pregnant or think you are pregnant during treatment with RETEVMO.
- If you are breastfeeding or planning to breastfeed: it is not known if RETEVMO passes into breast milk. Do not breastfeed during treatment with RETEVMO and for at least 2 weeks after your final dose. Talk to your healthcare professional about the best way to feed your baby during this time.

Male patients with female partners who are able to become pregnant:

- Use highly effective birth control while you are on RETEVMO and for at least 2 weeks after your last dose.
- If during your treatment with RETEVMO, your sexual partner becomes pregnant or thinks she may be pregnant, tell your healthcare professional right away.

Fertility: Taking RETEVMO may affect fertility in males and females. This means that it may be difficult for you to have a child. Talk to your healthcare professional if you have questions about this.

Driving and Using Machines: Fatigue and dizziness can occur with RETEVMO. Be cautious after taking RETEVMO to see how you feel before driving a vehicle or using machinery.

Children and adolescents:

- RETEVMO is not approved for the treatment of lung cancer or thyroid cancer other than medullary thyroid cancer in patients under 18 years of age.
- For the treatment of medullary thyroid cancer, RETEVMO is not approved for use in children under 12 years of age.

- Taking RETEVMO may cause slowed growth in children 12 to 17 years of age.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with RETEVMO:

- Alfentanil – used to treat pain
- Amphotericin B – used to treat fungal infections
- Avanafil – used to treat erectile dysfunction
- Bosentan, diltiazem, verapamil – used to treat high blood pressure and heart arrhythmias
- Buprenorphine – used to treat pain and help people stop taking pain medication
- Bupropion – used to treat depression and to help people stop smoking
- Buspirone – used to treat anxiety
- Carbamazepine – used to treat seizures, nerve pain, and sometimes used to treat bipolar disorders
- Ciprofloxacin, clarithromycin – used to treat bacterial infections
- Conivaptan – used to treat low sodium levels in the blood
- Dabigatran – used to prevent blood clots
- Darifenacin – used to treat a frequent need to urinate
- Darunavir, efavirenz, ritonavir, tipranavir – used to treat human immunodeficiency virus (HIV) infection
- Dexamethasone and other corticosteroids – used to treat asthma, severe allergies, certain lung diseases, a number of skin diseases, brain and eye swelling, and certain forms of arthritis. Dexamethasone may also be used to treat certain types of cancers.
- Dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, cimetidine, famotidine, nizatidine, aluminum hydroxide gel, subsalicylate, calcium carbonate, magnesium hydroxide, ranitidine – used to treat too much stomach acid
- Enzalutamide – used to treat prostate cancer
- Everolimus – used to treat cancer
- Fluconazole, itraconazole, ketoconazole, miconazole, posaconazole, voriconazole, rifampin, rifabutin – used to treat fungal and bacterial infections
- Ibrutinib – used to treat cancer
- Lomitapide, lovastatin, simvastatin – used to treat high cholesterol
- Midazolam – used for sedation and to treat anxiety
- Montelukast – used to treat asthma
- Naloxegol – used to treat constipation caused by some pain medications
- Paclitaxel – used to treat a number of different cancers

- Phenobarbital, phenytoin – used to prevent and control seizures
- Repaglinide, rosiglitazone, pioglitazone – used to treat diabetes
- Sorafenib – used to treat cancer
- Selexipag – used to treat pulmonary arterial hypertension
- St. John's Wort – an herbal medicine used to treat depression
- Telithromycin – used to treat certain types of bacterial infection
- Triazolam – used to help with sleeping
- Vardenafil – used to treat erectile dysfunction
- Medicines that cause heart rhythm conditions, including QT prolongation or torsade de pointes
- Medicines that cause a decrease in electrolyte levels. This includes:
    - diuretics (used to remove water from the body)
    - laxatives (used to loosen stools and increase bowel movements)
    - enemas (used to empty the bowels)
- Medicines that cause a decrease in heart rate. This includes:
    - beta-blockers (used to lower blood pressure)
    - digitalis glycosides (such as digoxin; used to treat congestive heart failure and abnormal heart rhythms)
    - calcium channel blockers (such as diltiazem and verapamil; used to lower blood pressure)
    - cholinesterase inhibitors (used to treat Alzheimer's and dementia symptoms)
    - alpha2-adrenoceptor agonists (used to treat high blood pressure, irregular heart rate, sedation, and the inability to feel pain)
    - I_f inhibitors (used to treat heart failure)
    - sphingosine-1 phosphate receptor modulators (used to treat multiple sclerosis)
- Products with grapefruit

Ask your doctor or pharmacist if you are not sure whether your medicine is one of the medicines listed above.

How to take RETEVMO:

- Take exactly as prescribed for you by your doctor. Do not change your dose or stop taking RETEVMO unless your doctor tells you to. Check with your doctor or pharmacist if you are not sure.
- RETEVMO is taken twice a day. Take at about the same time every day, about 12 hours apart.
- Swallow RETEVMO whole. Do not open, crush, or chew the capsule.
- Take with or without food, unless you are also taking a proton pump inhibitor (see next

bullet point).

- During treatment with RETEVMO, you should avoid taking medicines to treat stomach-acid issues called proton pump inhibitors, H2 blockers and antacids. These medicines can affect how RETEVMO works. If this cannot be avoided and you need to take:
    - a proton pump inhibitor (such as dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole sodium, and rabeprazole): then, take RETEVMO with food.
    - an H2 blocker (such as famotidine, nizatidine, and cimetidine): then, take RETEVMO 2 hours before or 10 hours after the H2 blocker.
    - an antacid (such as calcium carbonate, magnesium hydroxide, and simethicone): then, take RETEVMO 2 hours before or 2 hours after taking the antacid.

Usual dose:

The usual dose depends on your body weight. Your doctor will determine the right dose for you.

- For patients weighing less than 50 kg, the usual dose is: 120 mg twice a day. This is a total daily dose of 240 mg.
- For patients weighing 50 kg or greater, the usual dose is: 160 mg twice a day. This is a total dose of 320 mg.

Your doctor may interrupt, change, or stop your dose. This may occur:

- based on your current health,
- if you take certain other medications,
- if your disease gets worse,
- if you develop certain side effects, or
- you are having surgery.

Overdose:

If you think you, or a person you are caring for, have taken too much RETEVMO, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose and it is more than 6 hours until your next scheduled dose, take the missed dose as soon as you remember. Then continue with your next dose at your regular time.
- If it is within 6 hours of your next dose, skip the missed dose. Wait and take your next dose at your scheduled time. Do not take an extra dose.
- If you vomit after taking a dose, do not take an extra dose. Take your next dose at your regular time.

What are possible side effects from using RETEVMO?

These are not all the possible side effects you may have when taking RETEVMO. If you experience any side effects not listed here, tell your healthcare professional.

- Dry mouth, diarrhea, constipation, nausea, abdominal pain, vomiting
- Swelling in the stomach, arms, legs, hands, feet, eyes, face or other parts of your body
- Difficulty emptying your bladder, involuntary leakage of urine
- Fatigue, tiredness
- Decreased appetite
- Body pain, bone pain
- Headache, dizziness, ringing in the ears
- Cough, difficulty swallowing, shortness of breath
- Runny and stuffed nose, itchy eyes, sneezing, flushed and hot skin
- Skin rash, dry skin, skin sores or open wounds
- Confusion
- Erectile dysfunction
- Muscle pain, stiffness, weakness, cramps
- Feeling anxious, sad mood, difficulty sleeping, decreased sexual desire

RETEVMO can cause abnormal ECG and blood test results. ECG stands for electrocardiogram. Your doctor will do some tests before and during your treatment. These include checking for heart and liver problems and electrolyte levels in your blood. The doctor will interpret the results. They will tell you if there are any abnormalities in your tests that might need treatment.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Hypertension (high blood pressure)**:** headache, nosebleeds, shortness of breath, dizziness, chest pain, confusion.		✓	
Leukopenia, neutropenia, lymphopenia (low white blood cells)**:** chills, fever, infection. fatigue, aches and pains, and flu-like symptoms.		✓	

Liver problems and increased liver enzymes: loss of appetite, feeling sick or being sick, yellow skin, itching or pain in your liver area, yellowing of your skin and/or the white part of your eyes (jaundice), dark “tea-colored” urine, sleepiness, bleeding or bruising, loss of appetite, nausea or vomiting, pain on the upper right side of stomach.		✓	
QT Prolongation (a heart rhythm condition)**:** a change in the way your heart beats (palpitations), dizziness, shortness of breath, chest pain, fainting, loss of consciousness, seizures.		✓	
Thrombocytopenia (low blood platelets)**:** bruising or bleeding for longer than usual if you hurt yourself, tiredness, weakness, vomiting blood or if your vomit looks like coffee grounds, pink or brown urine, red or black (looks like tar) stools, coughing up blood or blood clots, unusual bleeding or bruising of your skin, menstrual bleeding that is heavier than normal, unusual vaginal bleeding, nose bleeds that happen often, drowsiness or difficulty being awakened, confusion, headache, change in speech.		✓	
Urinary tract infections: pain or burning sensation when peeing, need to pee more often than usual, pee that looks cloudy, blood in pee, feeling hot and shivery, pain in the lower stomach and back.		✓	
COMMON			
Allergic reactions: fever, rash, muscle or joint pain.			✓

Anemia (low red blood cells): Being short of breath, feeling very tired, loss of energy, weakness, chest pain, headache, dizziness, feeling light-headed.		✓	
Eye problems: dry eye, eye swelling, blurry vision.		✓	
Heart problems, including: • Chest discomfort or pain • **Cardiac arrhythmias/ palpitations:** fast, slow or irregular heartbeat, heart racing, skipping beats, shortness of breath, weakness, inability to exercise, fluid in the legs. • **Pericardial effusion** (fluid around the heart): sharp, piercing chest pain over the centre or left side of the chest, which is more intense when breathing in, shortness of breath, palpitations, fever, fatigue, weakness or feeling sick, cough, swelling in the abdomen or leg. • **Cardiac arrest** (heart stops beating): sudden collapse, no pulse, no breathing, loss of consciousness.			✓
Hyperthyroidism (overactive thyroid gland)**:** weight loss, rapid or irregular heartbeat, increased appetite, anxiety.		✓	
Hypothyroidism (underactive thyroid gland)**:** fatigue, increased sensitivity to cold, constipation, dry skin, weight gain.		✓	

Infections, including of the eye, nose, tooth, mouth, sinuses, throat, lungs, air passages, skin, stomach, intestines, blood: Fever and chills, fast heartbeat, nausea and vomiting, diarrhea, fatigue or weakness, discolored skin, sweating, severe pain, cough, shortness of breath, sharp chest pain, and rapid breathing.		✓	
Nervous system disorders: amnesia, decreased attention, memory problems, decreased sense of taste, numbness, burning sensation, feeling light-headed, fainting, seizure, tremor.		✓	
Respiratory (breathing) disorders, including: • **Pleural effusion** (fluid around your lungs) • **Pneumonitis** (inflammation of the lung tissue) • **Pulmonary embolism** (blood clot in the lungs) • **Respiratory failure** (stop breathing) Symptoms include: changes in your voice, shortness of breath, chest pain, nose bleed, coughing up blood, nasal congestion and dryness, cough, sore throat, pain in ear, runny nose, bluish color around skin of fingernails and lips.		✓	
Skin disorders: acne, hair loss, dry or flaky skin, itching, rash, reddening of the skin, extra sensitivity to the sun, excessive sweating, redness or swelling on the palms of the hands and soles of the feet.		✓	

LESS COMMON			
Chylothorax (build-up of chyle (lymphatic fluid) in the space around the lung) **and chylous ascites** (build-up of chyle in the space around the abdomen): shortness of breath, cough, chest discomfort, or trouble breathing.		✓	
Embolism (blockage in a blood vessel): Sudden shortness of breath, chest pain, coughing up blood, fainting, falling down, changes to your eyesight, numbness and tingling in your arms or legs, rapid breathing, rapid heart rate, muscle weakness.			✓
Gastrointestinal disorders: stomach pain, diarrhea often with blood, rectal bleeding and pain, weight loss, fatigue, nausea, vomiting, fever, difficulty swallowing, sore throat, cough, chest pain, pain in gums, mouth sores.		✓	
Hemorrhage (severe bleeding; blood loss): very low blood pressure, rapid heart rate, cold clammy skin, weakened pulse, fatigue, tingling or numbness in arms or legs, changes to vision, changes to balance, fainting, sudden severe headache, difficulty speaking, nausea, vomiting.		✓	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up).		✓	
Kidney failure/Acute kidney injury: Pee less, swelling in your legs, ankles or feet, short of breath, chest pain, muscle cramps, confusion, nausea,			✓

weakness, skin rashes, irregular heartbeat.			
Tumor lysis syndrome (the sudden, rapid death or breakdown of cancer cells due to treatment): nausea, shortness of breath, irregular heartbeat, heart rhythm disturbances, pee less, cloudy pee, muscle spasms or twitching, tiredness, joint pain, severe muscle weakness, seizures.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store RETEVMO at room temperature (15°C to 30°C).
- Do not use this medicine after the expiry date (EXP) shown on the bottle.
- Keep out of reach and sight of children.

If you want more information about RETEVMO:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by calling 1-888-545-5972.

This leaflet was prepared by Loxo Oncology, Inc.

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