Retevmo® (selpercatinib)

Treatment Plan Guide

INDICATIONS[1]

Retevmo is a kinase inhibitor indicated for the treatment of:

- adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *rearranged during transfection (RET)* gene fusion, as detected by an FDA-approved test
- adult and pediatric patients 12 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation, as detected by an FDA-approved test, who require systemic therapy*
- adult and pediatric patients 12 years of age and older with advanced or metastatic thyroid cancer with a *RET* gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)*
- adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options*

*These indications are approved under accelerated approval based on overall response rate (ORR) and duration of response (DoR). Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

Disclaimer: This guide is intended to provide information to develop a drug record for Retevmo and/or to assist users with creating a standard treatment template for use of Retevmo in the treatment of adult patients with locally advanced or metastatic NSCLC with a *RET* gene fusion, as detected by an FDA-approved test OR adult and pediatric patients 12 years of age and older with advanced or metastatic MTC with a *RET* mutation, as detected by an FDA-approved test, who require systemic therapy OR adult and pediatric patients 12 years of age and older with advanced or metastatic thyroid cancer with *a RET* gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate) OR adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options. Patients should be evaluated by a physician prior to the use of Retevmo and deemed to meet both a confirmatory diagnosis of any of the above indications and be an appropriate candidate for the use of Retevmo. Based on individual patient cases and unique scenarios, additional tests, assessments, and medications may be necessary for the proper care and treatment of patients receiving this regimen. This guide does not constitute a final order and may not meet the comprehensive needs of individual patients or institutions.

IMPORTANT SAFETY INFORMATION FOR RETEVMO

Hepatotoxicity: Serious hepatic adverse reactions occurred in 3% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 59% of patients, including Grade 3 or 4 events in 11% and increased alanine aminotransferase (ALT) occurred in 55% of patients, including Grade 3 or 4 events in 12%. Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity.

Severe, life-threatening, and fatal **interstitial lung disease (ILD)/pneumonitis** can occur in patients treated with Retevmo. ILD/pneumonitis occurred in 1.8% of patients who received Retevmo, including 0.3% with Grade 3 or 4 events, and 0.3% with fatal reactions. Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold Retevmo and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose, or permanently discontinue Retevmo based on severity of confirmed ILD.

Please see additional Important Safety Information throughout and click for full Prescribing Information for Retevmo.

Lilly

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selpercatinib capsules
40 mg • 80 mg

Pharmacology[1]

Class	*RET* kinase inhibitor
Mechanism of Action	Kinase inhibitor of *RET* (and other kinases)

Treatment[1]

Category	Details
Regimen	Retevmo days 1-30
FDA-Approved Indication	Retevmo is a kinase inhibitor indicated for the treatment of: • adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *rearranged during transfection (RET)* gene fusion, as detected by an FDA-approved test • adult and pediatric patients 12 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation, as detected by an FDA-approved test, who require systemic therapy* • adult and pediatric patients 12 years of age and older with advanced or metastatic thyroid cancer with a *RET* gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)* • adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options* *These indications are approved under accelerated approval based on overall response rate (ORR) and duration of response (DoR). Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.
Patient Selection	Patient selection for treatment with Retevmo should be based on the presence of a *RET* gene fusion (NSCLC, thyroid cancer, or other solid tumors) or specific *RET* gene mutation (MTC) in tumor specimens or plasma. Information on FDA-approved test(s) for the detection of *RET* gene fusions and *RET* gene mutations is available at: http://www.fda.gov/CompanionDiagnostics.

Treatment Medication[1]

Dosing	**Recommended starting dose** The recommended dosage of Retevmo based on body weight is†: • <50 kg: 120 mg PO BID • ≥50 kg: 160 mg PO BID
Dosage Forms and Strength	Retevmo is available in bottles as 80-mg and 40-mg capsules dispensed in 30-day supplies based on BID oral administration

Treatment Schedule[1]

Treatment Days	Daily
Cycle Length	30 days
Treatment Duration	Continuously until disease progression or unacceptable toxicity

†Dose interruptions and/or dose reductions may be required based on individual safety and tolerability. Refer to the full Prescribing Information for more complete information.
BID=twice daily; FDA=US Food and Drug Administration; PO=orally.

IMPORTANT SAFETY INFORMATION FOR RETEVMO (CONTINUED)

Hypertension occurred in 41% of patients, including Grade 3 hypertension in 20% and Grade 4 in one (0.1%) patient. Overall, 6.3% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity.

Please see additional Important Safety Information throughout and click for full Prescribing Information for Retevmo.

Monitoring[1]

Clinical Assessment	Laboratory and other clinical tests may be ordered more frequently at the discretion of the provider or according to institutional standards. • **Hepatotoxicity:** Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated • **ILD/Pneumonitis:** Monitor for pulmonary symptoms indicative of ILD/pneumonitis • **Hypertension:** Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated • **QT interval prolongation:** – Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes, and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia, and hypocalcemia prior to initiating Retevmo and during treatment – Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval • **Hypothyroidism:** Monitor thyroid function before treatment with Retevmo and periodically during treatment. Treat with thyroid hormone replacement as clinically indicated • **Assess patients for the following:** – **Hemorrhagic events** – **Hypersensitivity reactions** – **Tumor lysis syndrome (TLS)** – **Risk of impaired wound healing** – **Embryo-fetal toxicity** • **Potential consideration:** Consider alternative markers of renal function if persistent elevations in serum creatinine are observed. Serum creatinine increased 18% after 10 days in healthy volunteers given Retevmo 160 mg orally BID
Treatment Parameters	Labs and clinical assessments should be monitored to evaluate treatment, toxicity, and for dose modifications at the discretion of the treating provider. • **Hepatotoxicity:** Withhold, reduce dose, or permanently discontinue Retevmo based on the severity of ALT/AST increase • **ILD/Pneumonitis:** Withhold Retevmo and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose, or permanently discontinue Retevmo based on severity of confirmed ILD • **Hypertension:** Optimize blood pressure prior to initiating Retevmo. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity • **QT interval prolongation:** Withhold and dose reduce or permanently discontinue Retevmo based on the severity • **Hemorrhagic events:** Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage • **Hypersensitivity:** If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg prednisone (or equivalent). Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity • **TLS:** 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 • **Risk of impaired 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 • **Hypothyroidism:** Withhold Retevmo until clinically stable or permanently discontinue Retevmo based on severity • **Embryo-fetal toxicity:** Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the last dose

Administration Considerations[1]

Administration	• The recommended dosage of Retevmo based on body weight is: – <50 kg: 120 mg – ≥50 kg: 160 mg • Take Retevmo PO BID (approximately every 12 hours) until disease progression or until unacceptable toxicity • Swallow the capsules whole. Do not crush or chew the capsules • Do not take a missed dose unless it is more than 6 hours until next scheduled dose. If vomiting occurs after Retevmo administration, do not take an additional dose, and continue to the next scheduled time for the next dose
Food Interactions	• Retevmo may be taken with or without food • If coadministered with a proton pump inhibitor (PPI), take Retevmo with food
Dose Modifications	• Retevmo dose should be modified for hepatotoxicity, ILD/pneumonitis, hypertension, QT interval prolongation, hemorrhagic events, hypersensitivity reactions, hypothyroidism, and other adverse reactions (ARs) • Retevmo dose should be modified for concomitant use of acid-reducing agents, strong and moderate CYP3A inhibitors, and severe hepatic impairment

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CYP3A=cytochrome P450 3A; ILD=interstitial lung disease; TSH=thyroid-stimulating hormone.

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selpercatinib capsules
40 mg • 80 mg

How Supplied[1]

Capsule Strength	Quantity of Capsules per Bottle	NDC	Days' Supply
80 mg	120 count	0002-2980-26	**30 days (based on BID administration)**
80 mg	60 count	0002-2980-60	
40 mg	60 count	0002-3977-60	

Capsule Strength and Dosing Regimen: 30-Day Supply[1]

Target Dose	Dosage Modification: **Patient Weight ≥50 kg**	Dosage Modification: **Patient Weight <50 kg**	How Dispensed	Required Quantity of 80-mg 120-count Bottles	Required Quantity of 80-mg 60-count Bottles	Required Quantity of 40-mg 60-count Bottles
160 mg PO BID	Standard Dose	–	Two (2) 80-mg capsules BID	1	0	0
120 mg PO BID	First Dose Reduction	Standard Dose	Three (3) 40-mg capsules BID	0	0	3
80 mg PO BID	Second Dose Reduction	First Dose Reduction	One (1) 80-mg capsule BID	0	1	0
40 mg PO BID	Third Dose Reduction	Second Dose Reduction	One (1) 40-mg capsule BID	0	0	1
40 mg PO QD	–	Third Dose Reduction	One (1) 40-mg capsule QD	0	0	1*

*For 40-mg capsule QD dosing, dispensing a 40-mg 60-count bottle will provide a 60-day supply.

NDC=National Drug Code; QD=daily.

IMPORTANT SAFETY INFORMATION FOR RETEVMO (CONTINUED)

Retevmo can cause concentration-dependent **QT interval prolongation**. An increase in QTcF interval to >500 ms was measured in 7% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 20% of patients. Retevmo has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction. Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes, and thyroid-stimulating hormone (TSH) at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia, and hypocalcemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

Serious, including fatal, **hemorrhagic events** can occur with Retevmo. Grade ≥3 hemorrhagic events occurred in 3.1% of patients treated with Retevmo including 4 (0.5%) patients with fatal hemorrhagic events, including cerebral hemorrhage (n=2), tracheostomy site hemorrhage (n=1), and hemoptysis (n=1). Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

Hypersensitivity occurred in 6% of patients receiving Retevmo, including Grade 3 hypersensitivity in 1.9%. The median time to onset was 1.9 weeks (range: 5 days to 2 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis. If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg prednisone (or equivalent). Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity.

Please see additional Important Safety Information throughout and click for full Prescribing Information for Retevmo.

Dose Modifications/Reductions for ARs and Concomitant Use of Select Therapies[1]

AR	Severity	Dosage Modification
Hepatotoxicity	Grade 3 or Grade 4	• Withhold Retevmo and monitor AST/ALT once weekly until resolution to Grade 1 or baseline • Resume at a reduced dose by 2 dose levels and monitor AST and ALT once weekly until 4 weeks after reaching dose taken prior to the onset of Grade 3 or 4 increased AST or ALT • Increase dose by 1 dose level after a minimum of 2 weeks without recurrence and then increase to dose taken prior to the onset of Grade 3 or 4 increased AST or ALT after a minimum of 4 weeks without recurrence
ILD/Pneumonitis	Grade 2	• Withhold Retevmo until resolution • Resume at a reduced dose • Discontinue Retevmo for recurrent ILD/pneumonitis
	Grade 3 or Grade 4	• Discontinue Retevmo for confirmed ILD/pneumonitis
Hypertension	Grade 3	• Withhold Retevmo for Grade 3 hypertension that persists despite optimal antihypertensive therapy. Resume at a reduced dose when hypertension is controlled
	Grade 4	• Discontinue Retevmo
QT Interval Prolongation	Grade 3	• Withhold Retevmo until recovery to baseline or Grade 0 or 1 • Resume at a reduced dose
	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
Hypersensitivity Reactions	All Grades	• Withhold Retevmo until resolution of the event. Initiate corticosteroids • Resume at a reduced dose by 3 dose levels while continuing corticosteroids • Increase dose by 1 dose level each week until the dose taken prior to the onset of hypersensitivity is reached, then taper corticosteroids
Hypothyroidism	Grade 3 or Grade 4	• Withhold Retevmo until resolution to Grade 1 or baseline • Discontinue Retevmo based on severity
Other ARs	Grade 3 or Grade 4	• Withhold Retevmo until recovery to baseline or Grade 0 or 1 • Resume at a reduced dose

Dose Management for Concomitant Use		
Strong and Moderate CYP3A Inhibitors	• Avoid concomitant use of strong and moderate CYP3A inhibitors with Retevmo • If concomitant use of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the Retevmo dose	• If concomitant use of strong CYP3A inhibitors cannot be avoided, reduce Retevmo dose from 160 mg and 120 mg BID to 80 mg and 40 mg BID, respectively • If concomitant use of moderate CYP3A inhibitors cannot be avoided, reduce Retevmo dose from 160 mg and 120 mg BID to 120 mg and 80 mg BID, respectively
Acid-Reducing Agents	• Avoid concomitant use of a PPI, a histamine-2 (H2) receptor antagonist, or a locally-acting antacid with Retevmo	• If concomitant use cannot be avoided: – Take Retevmo with food when coadministered with a PPI – Take Retevmo 2 hours before or 10 hours after administration of an H2 receptor antagonist – Take Retevmo 2 hours before or 2 hours after administration of a locally-acting antacid

Reduce the recommended dosage of Retevmo for patients with severe hepatic impairment to 80 mg PO BID.

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Storage and Handling[1]

Strength[1]	80-mg and 40-mg capsules
Hazardous Classification[2]	• **Physical hazards:** not classified • **Health hazards:** reproductive toxicity (category 1B); specific target organ toxicity, single exposure (category 2); specific target organ toxicity, repeated exposure (category 2); germ cell mutagenicity (category 2) • **OSHA defined hazards:** combustible dust
Hazard Statement[2]	May form combustible concentrations in air H341: Suspected of causing genetic defects H360: May damage fertility or the unborn child H371: May cause damage to organs (bone marrow) H373: May cause damage to organs (gastrointestinal tract) through prolonged or repeated exposure
Storage	Keep Retevmo capsules at room temperature between 20°C to 25°C (68°F to 77°F); temperature excursions between 15°C and 30°C (59°F to 86°F) are permitted.[1] Keep container tightly closed in a dry and well-ventilated place.[2]
Precautions for Safe Handling[2]	Avoid contact with eyes, skin, and clothing
Disposal[2]	Dispose of contents/container in accordance with local/regional/national/international regulations
Stability and Reactivity[2]	• Reactivity: not water reactive • Chemical stability: material is stable under normal conditions • Possibility of hazardous reactions: hazardous polymerization does not occur

OSHA=Occupational Safety and Health Administration.

IMPORTANT SAFETY INFORMATION FOR RETEVMO (CONTINUED)

Tumor lysis syndrome (TLS) occurred in 0.6% 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.

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.

Retevmo can cause **hypothyroidism**. Hypothyroidism occurred in 13% of patients treated with Retevmo; all reactions were Grade 1 or 2. Hypothyroidism occurred in 13% of patients (50/373) with thyroid cancer and 13% of patients (53/423) with other solid tumors including NSCLC. Monitor thyroid function before treatment with Retevmo and periodically during treatment. Treat with thyroid hormone replacement as clinically indicated. Withhold Retevmo until clinically stable or permanently discontinue Retevmo based on severity.

Based on data from animal reproduction studies and its mechanism of action, Retevmo can cause **fetal harm** when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for 1 week after the last dose. There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Retevmo and for 1 week after the last dose.

Severe adverse reactions (Grade 3-4) occurring in ≥20% of patients who received Retevmo in LIBRETTO-001, were hypertension (20%), diarrhea (5%), prolonged QT interval (4.8%), dyspnea (3.1%), fatigue (3.1%), hemorrhage (2.6%), abdominal pain (2.5%), vomiting (1.8%), headache (1.4%), nausea (1.1%), constipation (0.8%), edema (0.8%), rash (0.6%), and arthralgia (0.3%).

Please see additional Important Safety Information throughout and click for full Prescribing Information for Retevmo.

Patient Counseling[1]

Administration	• The recommended dosage of Retevmo based on body weight is: – <50 kg: 120 mg – ≥50 kg: 160 mg • Take Retevmo PO BID (approximately every 12 hours) until disease progression or unacceptable toxicity • Retevmo may be taken with or without food • If coadministered with a PPI, take Retevmo with food • Swallow the capsules whole. Do not crush or chew the capsules • Do not take a missed dose unless it is more than 6 hours until next scheduled dose. If vomiting occurs after Retevmo administration, do not administer an additional dose and continue to the next scheduled time for the next dose
Drug Interactions*	• **Acid-reducing agents:** Avoid concomitant use of PPIs, H2 receptor antagonists, and locally-acting antacids with Retevmo. If coadministration cannot be avoided, take Retevmo with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally-acting antacid) • **Strong and moderate CYP3A4 inhibitors:** Avoid concomitant use of strong and moderate CYP3A inhibitors with Retevmo. If concomitant use of strong and moderate CYP3A inhibitors cannot be avoided, reduce the Retevmo dosage and monitor the QT interval with ECGs more frequently • **Strong and moderate CYP3A4 inducers:** Avoid coadministration of strong or moderate CYP3A4 inducers with Retevmo • **CYP2C8 and CYP3A substrates:** Avoid coadministration of Retevmo with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased ARs. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling • **P-gp substrates:** Avoid coadministration of Retevmo with P-gp substrates where minimal concentration changes may lead to increased ARs. If coadministration cannot be avoided, follow recommendations for P-gp substrates provided in their approved product labeling
ARs and Laboratory Abnormalities	• The most common ARs (≥25%) were edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, and headache • The most common Grade 3 or 4 laboratory abnormalities (≥5%) were decreased lymphocytes, increased ALT, increased AST, decreased sodium and decreased calcium • Serious adverse reactions occurred in 44% of patients who received Retevmo. The most frequent serious adverse reactions (≥2% of patients) were pneumonia, pleural effusion, abdominal pain, hemorrhage, hypersensitivity, dyspnea, and hyponatremia • Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions included sepsis (n=6), respiratory failure (n=5), hemorrhage (n=4), pneumonia (n=3), pneumonitis (n=2), cardiac arrest (n=2), sudden death (n=1), and cardiac failure (n=1) • Permanent discontinuation due to an AR occurred in 8% of patients who received Retevmo. ARs resulting in permanent discontinuation in ≥0.5% of patients included increased ALT (0.6%), fatigue (0.6%), sepsis (0.5%), and increased AST (0.5%) • Dose interruptions due to an AR occurred in 64% of patients who received Retevmo. ARs requiring dosage interruption in ≥5% of patients included increased ALT, increased AST, diarrhea, and hypertension • Dose reductions due to an AR occurred in 41% of patients who received Retevmo. ARs requiring dosage reduction in ≥2% of patients included increased ALT, increased AST, QT prolongation, fatigue, diarrhea, drug hypersensitivity, and edema

*This does not reflect the full list of drug interactions. Please see full accompanying Prescribing Information for Retevmo.

ECG=electrocardiogram; P-gp=P-glycoprotein.

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IMPORTANT SAFETY INFORMATION FOR RETEVMO (CONTINUED)

Serious adverse reactions occurred in 44% of patients who received Retevmo. The most frequently reported serious adverse reactions (in ≥2% of patients) were pneumonia, pleural effusion, abdominal pain, hemorrhage, hypersensitivity, dyspnea, and hyponatremia.

Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions included sepsis (n=6), respiratory failure (n=5), hemorrhage (n=4), pneumonia (n=3), pneumonitis (n=2), cardiac arrest (n=2), sudden death (n=1), and cardiac failure (n=1).

Common adverse reactions (all grades) occurring in ≥20% of patients who received Retevmo in LIBRETTO-001, were edema (49%), diarrhea (47%), fatigue (46%), dry mouth (43%), hypertension (41%), abdominal pain (34%), rash (33%), constipation (33%), nausea (31%), headache (28%), cough (24%), vomiting (22%), dyspnea (22%), hemorrhage (22%), arthralgia (21%), and prolonged QT interval (21%).

Laboratory abnormalities (all grades ≥20%; Grade 3-4) worsening from baseline in patients who received Retevmo in LIBRETTO-001, were increased AST (59%; 11%), decreased calcium (59%; 5.7%), increased ALT (56%; 12%), decreased albumin (56%; 2.3%), increased glucose (53%; 2.8%), decreased lymphocytes (52%; 20%), increased creatinine (47%; 2.4%), decreased sodium (42%; 11%), increased alkaline phosphatase (40%; 3.4%), decreased platelets (37%; 3.2%), increased total cholesterol (35%; 1.7%), increased potassium (34%; 2.7%), decreased glucose (34%; 1.0%), decreased magnesium (33%; 0.6%), increased bilirubin (30%; 2.8%), decreased hemoglobin (28%; 3.5%), and decreased neutrophils (25%; 3.2%).

Concomitant use of **acid-reducing agents** decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid concomitant use of proton-pump inhibitors (PPIs), histamine-2 (H2) receptor antagonists, and locally-acting antacids with Retevmo. If coadministration cannot be avoided, take Retevmo with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally-acting antacid).

Concomitant use of **strong and moderate CYP3A inhibitors** increases selpercatinib plasma concentrations which may increase the risk of Retevmo adverse reactions including QTc interval prolongation. Avoid concomitant use of strong and moderate CYP3A inhibitors with Retevmo. If concomitant use of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the Retevmo dosage as recommended and monitor the QT interval with ECGs more frequently.

Concomitant use of **strong and moderate CYP3A inducers** decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid coadministration of Retevmo with strong and moderate CYP3A inducers.

Concomitant use of Retevmo with **CYP2C8 and CYP3A substrates** increases their plasma concentrations which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of Retevmo with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

Retevmo is a P-glycoprotein (P-gp) inhibitor. Concomitant use of Retevmo with **P-gp substrates** increases their plasma concentrations, which may increase the risk of adverse reactions related to these substrates. 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.

The safety and effectiveness of Retevmo have not been established in **pediatric patients less than 12 years of age**. The safety and effectiveness of Retevmo have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced *RET* fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of Retevmo for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older. Monitor open growth plates in **adolescent patients**. Consider interrupting or discontinuing Retevmo if abnormalities occur.

No dosage modification is recommended for patients with **mild to severe renal impairment** (estimated Glomerular Filtration Rate [eGFR] ≥15 to 89 mL/min, estimated by Modification of Diet in Renal Disease [MDRD] equation). A recommended dosage has not been established for patients with end-stage renal disease.

Reduce the dose when administering Retevmo to patients with **severe hepatic impairment** (total bilirubin greater than 3 to 10 times upper limit of normal [ULN] and any AST). No dosage modification is recommended for patients with mild or moderate hepatic impairment. Monitor for Retevmo-related adverse reactions in patients with hepatic impairment.

Please click for full Prescribing Information for Retevmo.

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REFERENCES

1. Retevmo (selpercatinib). Prescribing Information. Lilly USA, LLC.

2. Retevmo (selpercatinib). Safety Data Sheet. Lilly USA, LLC.

Lilly

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