



Retevmo® (selpercatinib)

Treatment Plan Guide

INDICATIONS

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 2 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 2 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 and pediatric patients 2 years of age and older with locally advanced or metastatic solid tumors with a *RET* gene fusion, as detected by an FDA-approved test, that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options

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 2 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 2 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 and pediatric patients 2 years of age and older with locally advanced or metastatic solid tumors with a *RET* gene fusion, as detected by an FDA-approved test, 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® (selpercatinib)

Hepatotoxicity: Serious hepatic adverse reactions occurred in 4.6% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 62% of patients, including Grade 3 or 4 events in 11% and increased alanine aminotransferase (ALT) occurred in 58% of patients, including Grade 3 or 4 events in 13%. 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 severity.

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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 Indications	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 2 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 2 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 and pediatric patients 2 years of age and older with locally advanced or metastatic solid tumors with a RET gene fusion, as detected by an FDA-approved test, that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options
Patient Selection	Patient selection for treatment with Retevmo should be based on the presence of a RET gene fusion (NSCLC, thyroid cancer, or solid tumors) or specific RET gene mutation (MTC) in tumor specimens. 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. An FDA-approved companion diagnostic test for the detection of RET gene fusions and RET gene mutations in plasma is not currently available.

Dosing ¹		
Recommended Retevmo Dosage	Population	Retevmo Dosage*
	Adult and adolescent patients 12 years of age or older based on body weight	
	• Less than 50 kg	120 mg twice daily
	• 50 kg or greater	160 mg twice daily
	Pediatric patients 2 to less than 12 years of age based on body surface area	
	• 0.33 to 0.65 m ²	40 mg three times daily
	• 0.66 to 1.08 m ²	80 mg twice daily
	• 1.09 to 1.52 m ²	120 mg twice daily
	• ≥1.53 m ²	160 mg twice daily
	Dosing pediatric patients with body surface area less than 0.33 m ² is not recommended	
• Continue treatment with Retevmo until disease progression or unacceptable toxicity. • Swallow the capsule or tablet whole. Do not crush or chew the capsules or tablets. • For patients unable to swallow capsules or tablets or who are using a feeding tube, prepare and administer Retevmo as a dispersion; only Retevmo 40 mg tablets may be used to create the dispersion. • 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.		

*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.

Treatment Schedule ¹	
Treatment Days	Daily
Cycle Length	30 days
Treatment Duration	Continuously until disease progression or unacceptable toxicity

Important Safety Information for Retevmo® (selpercatinib) (Continued)

Severe, life-threatening, and fatal **interstitial lung disease (ILD)/pneumonitis** can occur in patients treated with Retevmo. ILD/pneumonitis occurred in 3% of patients who received Retevmo, including 0.3% with Grade 3 or 4 events, and 0.2% 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.

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Monitoring¹

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 – Slipped capital femoral epiphysis/slipped upper femoral epiphysis in pediatric patients • 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 that 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 • Slipped capital femoral epiphysis/slipped upper femoral epiphysis in pediatric patients: Monitor patients for symptoms indicative of SCFE/SUFE and treat as medically and surgically appropriate

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BID=twice daily; CYP3A=cytochrome P450 3A; ILD=interstitial lung disease; TLS=tumor lysis syndrome; TSH=thyroid-stimulating hormone.

Important Safety Information for Retevmo® (selpercatinib) (Continued)

Hypertension occurred in 43% of patients, including Grade 3 hypertension in 20% and Grade 4 in one (0.1%) patient. Overall, 6.4% had their dose interrupted, 1.5% had their dose reduced, and 0.2% discontinued Retevmo 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 severity.

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Administration Considerations¹

Administration	Population	Retevmo Dosage
	Adult and adolescent patients 12 years of age or older based on body weight	
	• Less than 50 kg	120 mg twice daily
	• 50 kg or greater	160 mg twice daily
	Pediatric patients 2 to less than 12 years of age based on body surface area	
	• 0.33 to 0.65 m ²	40 mg three times daily
	• 0.66 to 1.08 m ²	80 mg twice daily
	• 1.09 to 1.52 m ²	120 mg twice daily
	• ≥1.53 m ²	160 mg twice daily
	Dosing pediatric patients with body surface area less than 0.33 m ² is not recommended	
Food Interactions	- Continue treatment with Retevmo until disease progression or unacceptable toxicity. - Swallow the capsule or tablet whole. Do not crush or chew the capsules or tablets. - For patients unable to swallow capsules or tablets or who are using a feeding tube, prepare and administer Retevmo as a dispersion; only Retevmo 40 mg tablets may be used to create the dispersion. - 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.	
	- Retevmo may be taken with or without food. - If coadministered with a proton pump inhibitor (PPI), take Retevmo with food.	

Tablet Strength	Quantity of Tablets per Bottle	NDC
40 mg	60 count	0002-5340-60
80 mg	60 count	0002-6082-60
120 mg	60 count	0002-6120-60
160 mg	60 count	0002-5562-60

This chart details the difference between capsule dosing and tablet dosing

Dose	From (Capsules)	To (Tablets)
160-mg dose twice daily	2 x 80-mg capsules twice daily	1 x 160-mg tablet twice daily
120-mg dose twice daily	3 x 40-mg capsules twice daily	1 x 120-mg tablet twice daily
80-mg dose twice daily	1 x 80-mg capsule twice daily	1 x 80-mg tablet twice daily
40-mg dose twice daily	1 x 40-mg capsule twice daily	1 x 40-mg tablet twice daily

NDC=National Drug Code

Important Safety Information for Retevmo® (selpercatinib) (Continued)

Retevmo can cause concentration-dependent **QT interval prolongation**. An increase in QTcF interval to >500 ms was measured in 8% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 22% 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 4.3% of patients treated with Retevmo including 4 (0.5%) patients with fatal hemorrhagic events, including cerebral hemorrhage (n=2), tracheostomy site hemorrhage and hemoptysis (1 each). Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

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Dose modifications/reductions for ARs and concomitant use of select therapies¹

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 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 or permanently discontinue Retevmo
	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	Grades 1-3	- 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 corticosteroid - Discontinue Retevmo for any severe skin reaction including Stevens Johnson Syndrome.
	Recurrent Grade 3 or Grade 4	Discontinue Retevmo
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

ARs=Adverse reactions

Dose Management for Concomitant Use

Concomitant Use of CYP3A Inhibitors

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 as recommended in the table below. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume Retevmo at the dose taken prior to initiating the CYP3A inhibitor.

Current Retevmo Dosage	Recommended Retevmo Dosage	
	Moderate CYP3A Inhibitor	Strong CYP3A Inhibitor
40 mg orally three times daily	40 mg orally once daily	40 mg orally once daily
80 mg orally twice daily	40 mg orally twice daily	40 mg orally twice daily
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

Important Safety Information for Retevmo® (selpercatinib) (Continued)

Retevmo can cause **hypersensitivity**, including severe skin reactions such as Stevens-Johnson Syndrome. All grade hypersensitivity occurred in 6% of patients receiving Retevmo, including Grade 3 in 2%. The median time to onset was 1.9 weeks (range: 5 days to 6.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis. Stevens-Johnson Syndrome has been observed in the post-marketing setting.

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Concomitant Use with Acid-Reducing Agents

PPI	Take Retevmo with food when coadministered with a PPI
H2	Take Retevmo 2 hours before or 10 hours after administration of a H2 receptor antagonist.
Locally-acting antacid	Take Retevmo 2 hours before or 2 hours after administration of a locally-acting antacid

Dose Reduction for Severe Hepatic Impairment

Current Retevmo Dosage	Recommended Retevmo Dosage
40 mg orally three times daily	40 mg orally twice daily
80 mg orally twice daily	40 mg orally twice daily
120 mg orally twice daily	80 mg orally twice daily
160 mg orally twice daily	80 mg orally twice daily

Storage and Handling¹

Strength¹	40 mg and 80 mg capsules, or 40 mg, 80 mg, 120 mg and 160 mg tablets
Hazardous classification²	• 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 statement²	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 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 handling²	Avoid contact with eyes, skin, and clothing. ²
Disposal²	Dispose of contents/container in accordance with local/regional/national/international regulations
Stability and reactivity²	• 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® (selpercatinib) (Continued)

Discontinue Retevmo in patients with Stevens-Johnson Syndrome. 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.

Tumor lysis syndrome (TLS) occurred in 0.9% of patients with medullary thyroid carcinoma and 0.3% of patients with non-small cell lung cancer 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.

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Patient Counseling¹

Administration	Population	Retevmo Dosage
	Adult and adolescent patients 12 years of age or older based on body weight	
	• Less than 50 kg	120 mg twice daily
	• 50 kg or greater	160 mg twice daily
	Pediatric patients 2 to less than 12 years of age based on body surface area	
	• 0.33 to 0.65 m ²	40 mg three times daily
	• 0.66 to 1.08 m ²	80 mg twice daily
	• 1.09 to 1.52 m ²	120 mg twice daily
	• ≥1.53 m ²	160 mg twice daily
	Dosing pediatric patients with body surface area less than 0.33 m ² is not recommended	
	- Continue treatment with Retevmo until disease progression or unacceptable toxicity. - Swallow the capsules whole. Do not crush or chew the capsules. Do not administer to pediatric patients who are unable to swallow a capsule. - Swallow the tablets whole. Do not crush or chew the tablets. - 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.	
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 and BCRP substrates: Avoid coadministration of Retevmo with P-gp or BCRP substrates where minimal concentration changes may lead to increased ARs. If coadministration cannot be avoided, follow recommendations for P-gp and BCRP substrates provided in their approved product labeling	

*This does not reflect the full list of drug interactions. Please see full accompanying [Prescribing Information](#) for Retevmo.

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

Important Safety Information for Retevmo® (selpercatinib) (Continued)

Retevmo can cause **hypothyroidism**. Hypothyroidism occurred in 15% of patients treated with Retevmo; all reactions were Grade 1 or 2. Hypothyroidism occurred in 15% of patients (59/390) with thyroid cancer and 14% of patients (65/467) 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 embryoletality and malformations.

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Patient Counseling¹ (Continued)

Adverse Reactions and Laboratory Abnormalities

- The most common adverse reactions ($\geq 25\%$) were musculoskeletal pain, edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, rash, nausea, constipation, headache, vomiting, cough, dyspnea, and hemorrhage
- The most common Grade 3 or 4 laboratory abnormalities ($\geq 5\%$) were decreased lymphocytes, increased ALT, decreased sodium, increased AST, decreased calcium, and decreased phosphate
- Serious adverse reactions occurred in 58% of patients who received Retevmo. The most frequent serious adverse reactions ($\geq 2\%$ of patients) were pneumonia, hemorrhage, abdominal pain, dyspnea, pleural effusion, sepsis, musculoskeletal pain, hyponatremia, vomiting, diarrhea, and increased blood creatinine
- Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions included sepsis (n=6), respiratory failure (n=5), hemorrhage (n=4), pneumonia (n=4), cardiac arrest (n=3), pneumonitis (n=2), cardiac failure (n=2), sudden death (n=1), cerebral infarction (n=1), and dyspnea (n=1)
- Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received Retevmo. Adverse reactions resulting in permanent discontinuation in $\geq 0.5\%$ of patients included increased ALT (0.7%), fatigue (0.6%), sepsis (0.5%), pneumonia (0.5%), and increased AST (0.5%)
- Dosage interruptions due to an adverse reaction occurred in 72% of patients who received Retevmo. Adverse reactions requiring dosage interruption in $\geq 5\%$ of patients included increased ALT, increased AST, diarrhea, hypertension, and QT prolongation
- Dose reductions due to an adverse reaction occurred in 45% of patients who received Retevmo. Adverse reactions requiring dosage reductions in $\geq 2\%$ of patients included increased ALT, increased AST, fatigue, QT prolongation, diarrhea, drug hypersensitivity, and ascites

Important Safety Information for Retevmo® (selpercatinib) (Continued)

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.

Slipped capital femoral epiphysis/slipped upper femoral epiphysis in pediatric patients (SCFE/SUFE) occurred in 1 adolescent (2.8% of 36 patients) receiving Retevmo in LIBRETTO-121 and 1 adolescent patient (0.5% of 193 patients) receiving Retevmo in LIBRETTO-531. Monitor patients for symptoms indicative of SCFE/SUFE and treat as medically and surgically appropriate.

Severe adverse reactions (Grade 3-4) occurring in $\geq 20\%$ of patients who received Retevmo in LIBRETTO-001 were hypertension (20%), diarrhea (6.2%), prolonged QT interval (5%), fatigue (4.7%), musculoskeletal pain (4.1%), dyspnea (4.1%), hemorrhage (3.9%), abdominal pain (3.5%), vomiting (2.9%), urinary tract infection (2.2%), nausea (1.9%), headache (1.8%), edema (1.3%), decreased appetite (0.9%), constipation (0.8%), rash (0.8%), and dizziness (0.5%).

Severe adverse reactions (Grade 3-4) occurring in $\geq 15\%$ of patients who received Retevmo in LIBRETTO-121 were increased weight (11%), vomiting (8%), constipation (6%), diarrhea (2.8%), nausea (2.8%), upper respiratory tract infection (2.8%), and urinary tract infection (2.8%).

Severe adverse reactions (Grade 3-4) occurring in $\geq 15\%$ of patients who received Retevmo or chemotherapy with or without pembrolizumab in LIBRETTO-431 were hypertension (20% vs 3.1%), electrocardiogram QT prolonged (9% vs 0%), fatigue (3.2% vs 5%), edema (2.5% vs 0%), rash (1.9% vs 1.0%), diarrhea (1.3% vs 2.0%), abdominal pain (0.6% vs 2.0%), pyrexia (0.6% vs 0%), COVID19 infection (0.6% vs 0%), constipation (0% vs 1.0%), nausea (0% vs 1.0%), vomiting (0% vs 1.0%), and decreased appetite (0% vs 2.0%).

Severe adverse reactions (Grade 3-4) occurring in $\geq 10\%$ of patients who received Retevmo in LIBRETTO-531 were (Retevmo vs cabozantinib / vandetanib) hypertension (19% vs 18%), electrocardiogram QT prolonged (4.7% vs 2.1%), fatigue (4.1% vs 9%), diarrhea (3.1% vs 8%), rash (1.6% vs 4.1%), pyrexia (1.0% vs 0%), nausea (1.0% vs 5%), dry mouth (0.5% vs 1.0%), abdominal pain (0.5% vs 2.1%), stomatitis (0.5% vs 13%), headache (0.5% vs 0%), and decreased appetite (0.5% vs 5%).

Serious adverse reactions occurred in 58% of patients who received Retevmo in LIBRETTO-001. The most frequently reported serious adverse reactions (in $\geq 2\%$ of patients) were pneumonia, hemorrhage, abdominal pain, dyspnea, pleural effusion, sepsis, musculoskeletal pain, hyponatremia, vomiting, diarrhea, and increased blood creatinine. **Fatal adverse reactions occurred in 3% of patients in LIBRETTO-001;** fatal adverse reactions included sepsis (n=6), respiratory failure (n=5), hemorrhage (n=4), pneumonia (n=4), cardiac arrest (n=3), pneumonitis (n=2), cardiac failure (n=2), sudden death (n=1), cerebral infarction (n=1), and dyspnea (n=1).

Serious adverse reactions occurred in 42% of patients who received Retevmo in LIBRETTO-121. Serious adverse reactions occurring in more than 1 patient were vomiting and fracture (2 patients each).

Serious adverse reactions occurred in 35% of patients who received Retevmo in LIBRETTO-431.

The most frequently reported serious adverse reactions ($\geq 2\%$ of patients) were pleural effusion and abnormal hepatic function. **Fatal adverse reactions occurred in 4.4% of patients who received Retevmo in LIBRETTO-431;** fatal adverse reactions included myocardial infarction (n=2), respiratory failure (n=2), cardiac arrest, malnutrition, and sudden death (n=1 each).

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Important Safety Information for Retevmo® (selpercatinib) (Continued)

Serious adverse reactions occurred in 22% of patients who received Retevmo in LIBRETTO-531. The most frequent serious adverse reactions were pneumonia and pyrexia (n=3 each), and hypertension and urinary tract infection (n=2 each).

Fatal adverse reactions occurred in 2.1% of patients who received Retevmo in LIBRETTO-531; fatal adverse reactions included COVID19, diabetic ketoacidosis, multiple organ dysfunction syndrome, and sudden death (n=1 each).

Common adverse reactions (all grades) occurring in ≥20% of patients who received Retevmo in LIBRETTO-001, were musculoskeletal pain (59%), edema (53%), diarrhea (52%), fatigue (49%), dry mouth (44%), hypertension (43%), abdominal pain (39%), rash (38%), nausea (36%), constipation (35%), cough (30%), headache (30%), vomiting (29%), dyspnea (28%), hemorrhage (26%), decreased appetite (23%), dizziness (22%), prolonged QT interval (21%), and urinary tract infection (20%).

Common adverse reactions (all grades) occurring in ≥15% of patients who received Retevmo in LIBRETTO-121 were musculoskeletal pain (58%), diarrhea (47%), nausea (42%), hemorrhage (39%), pyrexia (39%), abdominal pain (36%), headache (33%), vomiting (31%), fatigue (31%), cough (31%), rash (28%), coronavirus infection (28%), upper respiratory tract infection (28%), edema (25%), constipation (22%), oropharyngeal pain (22%), hypothyroidism (22%), urinary tract infection (19%), and increased weight (19%).

Common adverse reactions (all grades) occurring in ≥15% of patients who received Retevmo or chemotherapy with or without pembrolizumab in LIBRETTO-431 were hypertension (48% vs 7%), diarrhea (44% vs 24%), edema (41% vs 28%), dry mouth (39% vs 6%), rash (33% vs 30%), fatigue (32% vs 50%), abdominal pain (25% vs 19%), musculoskeletal pain (25% vs 28%), constipation (22% vs 40%), electrocardiogram QT prolonged (20% vs 1.0%), COVID19 infection (19% vs 18%), stomatitis (18% vs 16%), decreased appetite (17% vs 34%), nausea (13% vs 44%), vomiting (13% vs 23%), and pyrexia (13% vs 23%).

Common adverse reactions (all grades) occurring in ≥10% of patients who received Retevmo in LIBRETTO-531 (Retevmo vs cabozantinib / vandetanib) were hypertension (43% vs 41%), edema (33% vs 5%), dry mouth (32% vs 10%), fatigue (28% vs 47%), diarrhea (26% vs 61%), headache (23% vs 21%), rash (19% vs 27%), abdominal pain (18% vs 21%), constipation (16% vs 12%), erectile dysfunction (16% vs 0%), stomatitis (14% vs 42%), electrocardiogram QT prolonged (14% vs 13%), pyrexia (12% vs 2.1%), decreased appetite (12% vs 28%), hypothyroidism (11% vs 21%), and nausea (10% vs 32%).

Laboratory abnormalities (all grades ≥20%; Grade 3-4) worsening from baseline in patients who received Retevmo in LIBRETTO-001, were increased AST (62%; 11%), decreased calcium (61%; 7%), decreased albumin (61%; 3.6%), increased ALT (58%; 13%), increased glucose (56%; 4.0%), decreased lymphocytes (56%; 22%), increased creatinine (51%; 3.6%), decreased sodium (49%; 13%), increased alkaline phosphatase (43%; 4.4%), decreased platelets (41%; 4.0%), increased potassium (39%; 3.5%), decreased glucose (39%; 1.5%), increased total cholesterol (37%; 1.7%), decreased magnesium (37%; 0.7%), decreased hemoglobin (36%; 4.1%), increased bilirubin (32%; 2.9%), decreased neutrophils (27%; 3.8%), and decreased phosphate (25%; 5%).

Laboratory abnormalities (all grades ≥15%; Grade 3-4) worsening from baseline in patients who received Retevmo in LIBRETTO-121 were decreased calcium (61%; 11%), increased ALT (58%; 8%), decreased albumin (53%; 0%), increased alkaline phosphatase (50%; 0%), increased AST (50%; 2.8%), increased bilirubin (31%; 2.8%), increased cholesterol (28%, 0%), decreased magnesium (28%; 6%), increased potassium (28%; 2.8%), increased creatinine (19%, 2.8%), decreased potassium (19%, 6%), decreased sodium (17%, 0%), decreased neutrophils (40%; 8%), decreased hemoglobin (36%; 11%), increased hemoglobin (33%, 2.8%), decreased platelets (28%; 2.8%), and decreased lymphocytes (28%; 14%).

Laboratory abnormalities (all grades ≥20%; Grade 3-4) worsening from baseline in patients who received Retevmo or chemotherapy with or without pembrolizumab in LIBRETTO-431 were increased ALT (81%; 21% vs 63%; 4.1%), increased AST (77%; 10% vs 46%; 0%), decreased calcium (53%; 1.9% vs 24%; 1.0%), decreased platelets (53%; 3.2% vs 39%; 5%), decreased lymphocytes (53%; 8% vs 64%; 15%), decreased neutrophils (53%; 2.0% vs 58%; 11%), increased bilirubin (52%; 1.3% vs 9%; 0%), increased alkaline phosphatase (35%; 1.3% vs 22%; 0%), decreased sodium (31%; 3.2% vs 41%; 2.1%), decreased albumin (25%; 0% vs 5%; 0%), increased blood creatinine (23%; 0% vs 21%; 0%), decreased hemoglobin (21%; 0% vs 91%; 5%), decreased potassium (17%; 1.3% vs 15%; 1.0%), and decreased magnesium (16%; 0.6% vs 8%; 0%).

Laboratory abnormalities (all grades ≥5%; Grade 3-4) worsening from baseline in patients who received Retevmo in LIBRETTO-531 (Retevmo vs cabozantinib / vandetanib) were decreased calcium (55%; 5% vs 62%; 11%), increased ALT (53%; 16% vs 72%; 7%), increased AST (47%; 5% vs 68%; 3.2%), decreased lymphocytes (41%; 18% vs 36%; 13%), increased alkaline phosphatase (37%; 6% vs 28%, 5%), increased bilirubin (32%; 1.1% vs 30%; 3.2%), decreased neutrophils (33%; 14% vs 42%; 19%), decreased platelets (28%; 1.1% vs 34%; 1.1%), increased creatinine (27%; 6% vs 16%; 8%), decreased sodium (20%; 3.2% vs 16%; 0%), decreased hemoglobin (18%; 2.1% vs 23%; 2.1%), decreased albumin (11%; 1.1% vs 7%; 0), magnesium decreased (9%; 3.3% vs 26%; 9%), and decreased potassium (8%; 0% vs 22%; 4.4%).

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).



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Important Safety Information for Retevmo® (selpercatinib) (Continued)

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

The safety and effectiveness of Retevmo have not been established in pediatric patients less than 2 years of age.

The safety and effectiveness of Retevmo have been established in pediatric patients aged 2 years and older for the treatment of advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation who require systemic therapy, advanced or metastatic thyroid cancer with a *RET* gene fusion who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate), and 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.

Monitor open growth plates in **pediatric 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.

Retevmo (selpercatinib) is available as 40 mg and 80 mg capsules, and 40 mg, 80 mg, 120 mg, and 160 mg tablets.

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REFERENCES

1. Retevmo (selpercatinib). Prescribing Information. Lilly USA, LLC.
2. Retevmo (selpercatinib). Safety Data Sheet. Indianapolis, IN: Eli Lilly and Company; 2024.

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