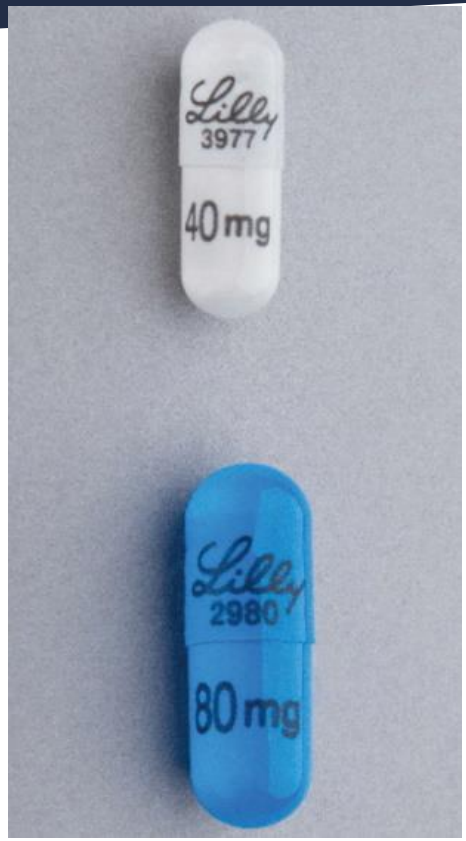
Retevmo (selpercatinib)



NEW PRODUCT SLIDESHOW

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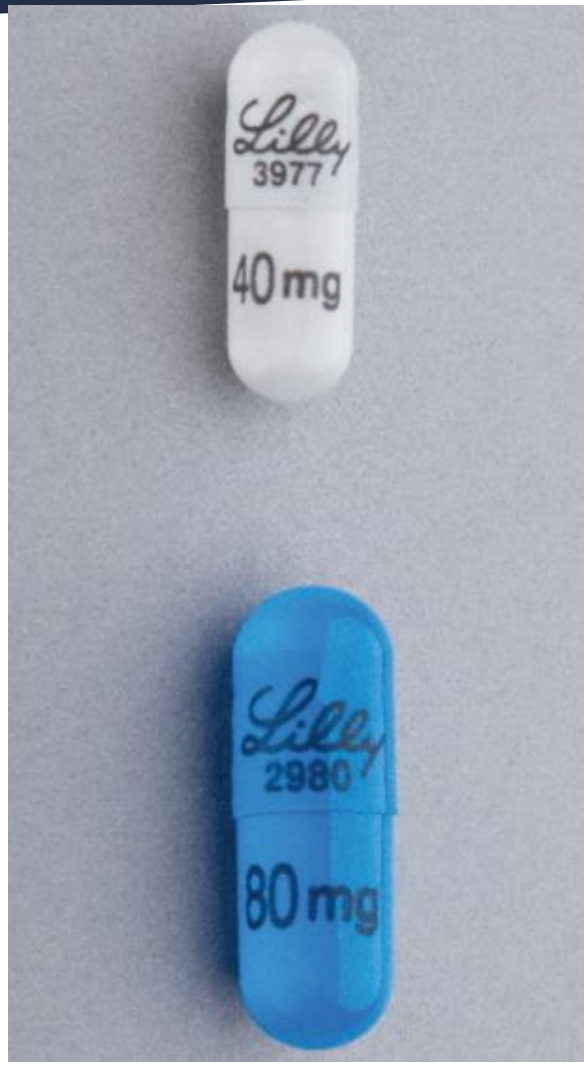
Introduction

- **Brand name:** Retevmo
- **Generic name:** Selpercatinib
- **Pharmacologic class:** Kinase inhibitor
- **Strength and Formulation:** 40mg, 80mg; hard gelatin capsules
- **Manufacturer:** Lilly
- **How supplied:** Caps 40mg—60; 80mg—60, 120
- **Legal Classification:** Rx

Retevmo



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Indication

- Adult patients with metastatic ***RET* fusion-positive non-small cell lung cancer** (NSCLC)
- Adult and pediatric patients 12 years of age and older with advanced or metastatic ***RET*-mutant medullary thyroid cancer** (MTC) who require systemic therapy
- Adult and pediatric patients 12 years of age and older with advanced or metastatic ***RET* fusion-positive thyroid cancer** who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)
  - Approved under accelerated approval based on overall response rate and duration of response
  - Continued approval may be contingent upon verification of clinical benefit in confirmatory trials

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Dosage and Administration

- **<12 years: not established**
- Select patients based on presence of a *RET* gene fusion (NSCLC or thyroid cancer) or specific *RET* gene mutation (MTC) in tumor specimens or plasma
- Swallow capsules whole
- <50kg: 120mg twice daily (approx. every 12hrs)
- ≥50kg: 160mg twice daily (approx. every 12hrs)
- Continue until disease progression or unacceptable toxicity
- Do not take a missed dose unless it is more than 6 hours until next scheduled dose

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Dosage Modifications for Concomitant Use of Acid-Reducing Agents

- Avoid concomitant use of a PPI, a histamine-2 (H_2) receptor antagonist, or a locally-acting antacid
- **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 H_2 receptor antagonist
  - Take Retevmo 2 hours before or 2 hours after administration of a locally-acting antacid

Dose Reductions for Adverse Reactions

Dose Reduction	Patients Weighing Less Than 50kg	Patients Weighing 50kg or Greater
First	80mg twice daily	120mg twice daily
Second	40mg twice daily	80mg twice daily
Third	40mg once daily	40mg twice daily

Permanently discontinue in patients unable to tolerate 3 dose reductions

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Dosage Modification for Adverse Reactions

Hepatotoxicity

- *Grade 3 or Grade 4*
  - Withhold 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

Dosage Modification for Adverse Reactions

Hypertension

- *Grade 3*
  - Withhold for Grade 3 hypertension that persists despite optimal antihypertensive therapy
  - Resume at reduced dose when hypertension controlled
- *Grade 4*
  - Discontinue

QT Interval Prolongation

- *Grade 3*
  - Withhold until recovery to baseline or Grade 0 or 1
  - Resume at reduced dose
- *Grade 4*
  - Discontinue

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Dosage Modification for Adverse Reactions

Hemorrhagic Events

- *Grade 3 or Grade 4*
  - Withhold until recovery to baseline or Grade 0 or 1
  - Discontinue for severe or life-threatening hemorrhagic events

Hypersensitivity Reactions

- *All Grades*
  - Withhold until resolution of event
  - Initiate corticosteroids
  - Resume at reduced dose by 3 dose levels while continuing corticosteroids
  - Increase dose by 1 dose level each week until dose taken prior to onset of hypersensitivity reached, then taper corticosteroids

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Dosage Modification for Adverse Reactions

Other Adverse Reactions

- *Grade 3 or Grade 4*
  - Withhold until recovery to baseline or Grade 0 or 1
  - Resume at reduced dose

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Recommended Dosage for Concomitant Use of Strong and Moderate CYP3A Inhibitors

Current Retevmo Dosage	Moderate CYP3A Inhibitor	Strong CYP3A Inhibitor
120mg twice daily	80mg twice daily	40mg twice daily
160mg twice daily	120mg twice daily	80mg twice daily

- Avoid concomitant use of strong and moderate CYP3A inhibitors
- If concomitant use cannot be avoided, reduce Retevmo dose
- After the inhibitor has been discontinued for 3-5 elimination half-lives, resume Retevmo at dose taken prior to initiating CYP3A inhibitor

Dosage Modification for Severe Hepatic Impairment

Current Retevmo Dosage	Recommended Retevmo Dosage
120mg twice daily	80mg twice daily
160mg twice daily	80mg twice daily

Considerations for Special Populations

- **Pregnancy:** can cause fetal harm
- **Nursing mothers**: not recommended during treatment and for 1 week after last dose
- **Pediatric**: not established for NSCLC indication
- **Geriatrics**: no overall differences in safety or effectiveness observed
- **Hepatic impairment**: see Dosing; reduce dose with severe impairment
- **Renal impairment**: not established in patients with severe impairment or ESRD

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Warnings/Precautions

- Risk of hepatotoxicity
- Monitor ALT/AST prior to initiation, every 2 weeks during 1st 3 months, then monthly thereafter and as clinically indicated
- Uncontrolled hypertension: do not initiate
- Optimize BP prior to initiation, monitor after 1 week, then at least monthly thereafter and as clinically indicated
- Monitor patients with significant risk of QTc prolongation (including known long QT syndromes, clinically significant bradyarrhythmias, severe or uncontrolled HF)
- Assess QT interval, electrolytes, TSH at baseline and periodically during treatment

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Warnings/Precautions

- Correct hypokalemia, hypomagnesemia, and hypocalcemia prior to initiation and during therapy
- Withhold if hypersensitivity occurs and begin corticosteroids
- Permanently discontinue if recurrent hypersensitivity, severe or life-threatening hemorrhage occurs
- Impaired wound healing: withhold for ≥7 days prior to elective surgery; do not give for ≥2 weeks after major surgery and until adequate healing
- Safety of resuming therapy after resolution of wound healing complications has not been established

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Warnings/Precautions

- Clinically significant active cardiovascular disease, recent MI: not studied
- Severe renal impairment (CrCl <30mL/min) or ESRD
- Severe hepatic impairment (total bilirubin >3–10×ULN and any AST): reduce dose (see Dosing)
- Embryo-fetal toxicity
- Advise females of reproductive potential and males (w. female partners) to use effective contraception during and for 1 week after the last dose
- May impair fertility in females and males of reproductive potential

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Interactions

- Potentiated by strong or moderate **CYP3A inhibitors**; avoid; if unavoidable, reduce dose (see Dosing), and monitor QT interval frequently
- Antagonized by strong or moderate **CYP3A inducers**; avoid
- Antagonized by **acid-reducing agents** (eg, PPIs, H_2-receptor antagonists, locally-acting antacids); avoid; if unavoidable (see Dosing)
- Potentiates **CYP2C8 and CYP3A substrates**; avoid; if unavoidable, follow recommendations for substrates (see respective product labeling)
- Concomitant with **drugs known to prolong QT** interval; obtain ECGs more frequently

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Adverse Reactions

- **Most frequent** (≥25%): increased AST, increased ALT, increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, constipation
- **Others**: hemorrhagic events

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Mechanism of Action

- Selpercatinib is a kinase inhibitor
- In *in vitro* and *in vivo* tumor models, selpercatinib demonstrated anti-tumor activity in cells harboring constitutive activation of RET protein resulting from gene fusions and mutations, including CCDC6-RET, KIF5B-RET, RET V804M, and RET M918T

Pharmacokinetics

- 97% protein bound
- Half-life: 32 hours
- Metabolized predominantly by CYP3A4
- Excreted in feces and urine

Clinical Trials

Metastatic *RET* Fusion-Positive NSCLC

- Open-label, multi-cohort study that enrolled patients with advanced or metastatic *RET* fusion-positive NSCLC who had progressed on platinum-based chemotherapy and patients with advanced or metastatic NSCLC without prior systemic therapy in separate cohorts
- Patients received Retevmo 160mg twice daily until unacceptable toxicity or disease progression
- Primary end points: confirmed overall response rate (ORR) and duration of response (DoR)

Clinical Trials

Metastatic *RET* Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy

- Efficacy evaluated in 105 patients; median age was 61 years; 59% female; 52% White
- Patients received a median of 3 prior therapies
- *RET* fusions detected in 90% of patients
- ORR was 64% (95% CI, 54-73) and median DoR was 17.5 months (95% CI, 12, not estimable [NE]), with 81% of patients having responses lasting ≥6 months
- For the 58 patients who received anti-PD-1 or anti-PD-L1 therapy, either sequentially or concurrently with platinum-based chemotherapy, exploratory subgroup analysis of ORR was 66% (95% CI, 52-78) and median DoR was 12.5 months (95% CI, 8.3, NE)

Clinical Trials

Treatment-Naïve *RET* Fusion-Positive NSCLC

- Efficacy evaluated in 39 patients; median age was 61 years; 56% female; 72% White
- *RET* fusions detected in 92% of patients
- ORR was 85% (95% CI, 70-94) and median DoR was NE (95% 12, NE), with 58% of patients having responses lasting ≥6 months

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Clinical Trials

RET-Mutant Medullary Thyroid Cancer Treated With Cabozantinib or Vandetanib

- Efficacy evaluated in 55 patients; median age was 57 years; 66% male; 89% White
- 98% had metastatic disease
- Patients received a median of 2 prior systemic therapies (range 1-8)
- *RET* mutations detected in 82% of patients
- ORR was 69% (95% CI, 55-81) and median DoR was NE (95% CI, 19.1, NE), with 76% of patients having responses lasting ≥6 months

Clinical Trials

Cabozantinib and Vandetanib-Naïve *RET*-Mutant Medullary Thyroid Cancer

- Efficacy evaluated in 88 patients; median age was 58 years; 66% male; 86% White
- All had metastatic disease
- 18% received 1 or 2 prior therapies
- *RET* mutations detected in 78.4% of patients
- ORR was 73% (95% CI, 62-82) and median DoR was 22 months (95% CI, NE, NE), with 61% of patients having responses lasting ≥6 months

Clinical Trials

RET Fusion-Positive Thyroid Cancer

- Efficacy evaluated in 27 patients with *RET* fusion-positive thyroid cancer who were radioactive iodine (RAI)-refractory (if RAI was an appropriate treatment option) and were systemic therapy naïve and patients with *RET* fusion-positive thyroid cancer who were RAI-refractory and had received sorafenib, lenvatinib, or both, in separate cohorts
- Median age was 54 years; 52% male; 74% White
- All had metastatic disease; patients received median 3 prior therapies (range 1-7)
- *RET* fusions detected in 93% of patients

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Clinical Trials

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

- **Previously treated** (n=19): ORR was 79% (95% CI, 54-94) and median DoR was 18.4 months (95% CI, 7.6, NE), with 87% of patients having responses lasting ≥6 months
- **Therapy Naïve** (n=8): ORR was 100% (95% CI, 63-100) and median DoR was NE (95% CI, NE, NE), with 75% of patients having responses lasting ≥6 months

New Product Monograph

- For more information view the product monograph available at:

  https://www.empr.com/drug/retevmo/