PDL DRUG REVIEW

Proprietary Name: Retevmo®
Common Name: selpercatinib
PDL Category: Antineoplastics

Summary

Pharmacology/Usage: Selpercatinib, the active ingredient of Retevmo®, is a kinase inhibitor that inhibits wild type RET and multiple mutated RET isoforms as well as VEGFR1 and VEGFR3.

Indication: For the treatment of

- 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).

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

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies and its mechanism of action, Retevmo® can cause fetal harm when administered to a pregnant woman. There are no available data on use in pregnant women to inform drug-associated risk. Advise pregnant women of the potential risk to the fetus. In addition, verify the pregnancy status of females of reproductive potential prior to starting Retevmo®, as well as advise them to use effective contraception (for females of reproductive potential and males with female partners of reproductive potential) during Retevmo® treatment and for 1 week after the last dose. The safety and efficacy of use in the pediatric population younger than 12 years of age have not been established, as well as for use at any age with *RET* fusion-positive NSCLC.

Dosage Form: Capsules: 40mg, 80mg. Swallow capsules whole; do not crush or chew the capsules.

Recommended Dosage: Select patients for treatment with Retevmo® based on the presence of a *RET* gene fusion (NSCLC or thyroid cancer) or specific *RET* gene mutation (MTC) in tumor specimens or plasma. An FDA-approved test for the detection of *RET* gene fusions and *RET* gene mutations is not currently available.

Take 120mg (if <50kg) or 160mg (if ≥50kg) PO BID until disease progression or unacceptable toxicity.

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 co-administered 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

Dose modifications may be required for adverse events, such as hepatotoxicity, hypertension, QT interval prolongation, hemorrhagic events, hypersensitivity reactions, or other adverse reactions. Refer to the prescribing information for further details.

Dose adjustments are not required with mild to moderate renal impairment. In addition, the recommended dosage has not been established for patients with severe renal impairment or end-stage renal disease. Dose reductions are required with severe hepatic impairment. If currently taking 120mg BID or 160mg BID, the recommended dose with severe hepatic impairment is 80mg BID. While dose adjustments are not required with mild or moderate hepatic impairment, it is recommended to monitor for Retevmo®-related adverse reactions in patients with hepatic impairment.

Drug Interactions: Retevmo® is associated with QTc interval prolongation. Monitor the QT interval with ECGs more frequently in patients who require treatment with concomitant medications that are known to prolong the QT interval.

Concomitant use of Retevmo® with acid-reducing agents decreases selpercatinib plasma concentrations. 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 administration time (with a H2 receptor antagonist or a local-acting antacid. Refer to the Recommended Dosage section).

Concomitant use of Retevmo® with a strong or moderate CYP3A inhibitor increases selpercatinib plasma levels. 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. Refer to the prescribing information for specific information.

Concomitant use of Retevmo® with a strong or moderate CYP3A inducer decreases selpercatinib plasma levels. Avoid coadministration of strong or moderate CYP3A inducers with Retevmo®.

Retevmo® is a moderate CYP2C8 inhibitor and a weak CYP3A inhibitor. Concomitant use of Retevmo® with CYP2C8 and CYP3A substrates increases their plasma concentrations. Avoid the co-administration of Retevmo® with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If co-administration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Retevmo®) for all grades. Please note that there is no placebo data in the prescribing information to compare with Retevmo®.* The most frequently reported adverse events included dry mouth (39%), diarrhea (37%), constipation (25%), nausea (23%), abdominal pain (23%), vomiting (15%), hypertension (35%), fatigue (35%), edema (33%), rash (27%), headache (23%), cough (18%), dyspnea (16%), prolonged QT interval (17%), and hemorrhage (15%).

Laboratory abnormalities included increased AST (51%), increased ALT (45%), increased glucose (44%), decreased albumin (42%), decreased calcium (41%), increased creatinine (37%), increased alkaline phosphatase (36%), increased total cholesterol (31%), decreased sodium (27%), decreased magnesium (24%), increased potassium (24%), increased bilirubin (23%), decreased glucose (22), decreased leukocytes (43%), and decreased platelets (33%).

Due to reports of serious hepatic adverse reactions with Retevmo® use, it is recommended to monitor ALT and AST prior to starting treatment, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated.

As hypertension has been reported in patients taking Retevmo®, do not start Retevmo® treatment in patients with uncontrolled hypertension. Optimize blood pressure prior to staring treatment. Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated. Start or adjust anti-hypertensive therapy as appropriate.

Retevmo® can cause concentration-dependent QT interval prolongation. Use 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 TSH at baseline and periodically during treatment. Correct hypokalemia, hypomagnesemia, and hypocalcemia prior to starting and during treatment.

Serious including fatal hemorrhagic events can occur with Retevmo®. Grade ≥3 hemorrhagic events occurred in 2.3% of patients treated with Retevmo®, including 0.4% with fatal hemorrhagic events.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Thus, 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 after major surgery and until adequate wound healing. The safety of resumption of Retevmo® after resolution of wound healing complications has not been established.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Eli Lilly

Analysis: The safety and efficacy of Retevmo® were assessed in patients with advanced *RET* fusion-positive NSCLC in a multicenter, open-label multicohort 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. The main efficacy outcomes were confirmed overall response rate (ORR) and duration of response (DOR).

The efficacy of Retevmo® was assessed in patients with *RET* fusion-positive NSCLC previously treated with platinum chemotherapy (N=105). The median age of included adults was 61 years, while 59% were female, 52% were white, and 98% had metastatic disease. Patients received a median of 3 prior systemic therapies. Results can be seen in the table below, which was adapted from the prescribing information.

Efficacy Outcome	Retevmo® (N=105)
Overall Response Rate	
Overall Response Rate	64%
Complete Response	1.9%
Partial Response	62%
Duration of Response	
Median in months	17.5
% with ≥6 months	81

For the 58 patients who received an anti-PD-1 or anti-PD-L1 therapy, either sequentially or concurrently with platinum-based chemotherapy, an exploratory subgroup analysis of ORR was 66% and the median DOR was 12.5 months. Of the 105 patients with *RET* fusion-positive NSCLC, 11 had measurable CNS metastases at baseline. No patients 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; all responders had DOR of ≥6 months.

The efficacy of Retevmo® was assessed in treatment naïve patients with *RET* fusion-positive NSCLC (N=39). The median age of included adults was 61 years, while 56% were female, 72% were white, and all patients had metastatic disease. Efficacy results can be seen in the table below, which was adopted from the prescribing information.

Efficacy Outcome	Retevmo® (N=39)
Overall Response Rate	
Overall Response Rate	85%
Complete Response	0%
Partial Response	85%
Duration of Response	
Median in months	Not estimable
% with ≥6 months	58

The efficacy of Retevmo® was assessed in patients with *RET*-mutant medullary thyroid cancer (MTC) in a multicenter, open-label, multicohort study that included patients with advanced or metastatic *RET*-mutant MTC who had been previously treated with cabozantinib or vandetanib (or both) and patients with advanced or metastatic *RET* mutant MTC who were naïve to cabozantinib and vandetanib in separate cohorts.

The efficacy of Retevmo® was assessed in patients with *RET* mutant advanced MTC who had previously been treated with cabozantinib or vandetanib (N=55). The median age of included adults was 57 years, while 66% were male, 89% were white, and 98% had metastatic disease. Patients received a median of 2 prior systemic therapies. Results can be seen in the table below, which was adapted from the prescribing information.

Efficacy Outcome	Retevmo® (N=55)
Overall Response Rate	
Overall Response Rate,	69%
Complete Response	9%
Partial Response	60%
Duration of Response	
Median in months	Not estimable
% with ≥6 months	76

The efficacy of Retevmo® was assessed in patients with *RET* mutant MTC who were cabozantinib and vandetanib treatment-naïve (N=88). The median age of included patients was 58 years (range 15 to 82 years) , while 66% were male, 86% were white, and all patients had metastatic disease. Results can be seen in the table below, which was adapted from the prescribing information.

Efficacy Outcome	Retevmo® (N=88)
Overall Response Rate	
Overall Response Rate	73%
Complete Response	11%
Partial Response	61%
Duration of Response	
Median in months	22
% with ≥6 months	61

The efficacy of Retevmo® was assessed in patients with advanced *RET* fusion-positive thyroid cancer in a multicenter, open-label, multicohort study that included patients with *RET* fusion-positive thyroid cancer who were radioactive iodine (RAI)-refractory 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. The median age of included patients was 54 years, while 52% were male, 74% were white, and all patients had metastatic disease. Patients had received a median of 3 prior therapies. Results can be seen in the table below, which was adapted from the prescribing information.

Efficacy Outcome	Retevmo® Previously treated (N=19)	Retevmo® Systemic therapy naïve (N=8)
Overall Response Rate		
Overall Response Rate	79%	100%
Complete Response	5.3%	12.5%
Partial Response	74%	88%
Duration of Response		
Median in months	18.4	Not estimable
% with ≥6 months	87	75

Place in Therapy: Retevmo is a kinase inhibitor indicated for metastatic *RET* fusion-positive non-small cell lung cancer, *RET* mutant medullary thyroid cancer, and *RET* fusion-positive thyroid cancer. Retevmo® can cause concentration-dependent QT interval prolongation. In the various studies, there has been an overall response rate of at least 64%.

It is recommended that Retevmo® should be non-recommended with conditions in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Retevmo [package insert]. Indianapolis, IN: Lilly; 2020.