Clinical Policy Title:	selpercatinib
Policy Number:	RxA.636
Drug(s) Applied:	Retevmo™
Original Policy Date:	09/14/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

Selpercatinib (Retevmo™) is a kinase inhibitor indicated 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).

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
selpercatinib (Revetmo™)	• 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).	Orally: twice a day Based upon body weight: • < 50kg: 120 mg/dose • ≥ 50kg: 160 mg/dose Severe hepatic impairment: Reduce the starting dose to 80 mg orally twice daily regardless of the original starting dose	• < 50 kg: 240 mg/day orally • ≥ 50 kg: 320 mg/day orally •

Dosage Forms

- Capsules: 40 mg, 80 mg.

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Non-Small Cell Lung Cancer or Medullary Thyroid Cancer

1. The member must have one of the following disease states:
   i. Adult patients with metastatic RET fusion-positive NSCLC;
   ii. Adult and pediatric patients ≥ 12 years with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy;
   iii. Adult and pediatric patients ≥ 12 years with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).
2. Prescribed by or in consultation with an oncologist;
3. The member must have an ECOG score of 0 or 1;
4. The member is ≥ 12 years of age;
5. Maximum Dose does not exceed (a or b):
   a. 240 mg per day for < 50 kg weight;
   b. 320 mg per day for ≥ 50 kg weight;

Approval Duration
Commercial: 3 months
Medicaid: 3 months

B. Histiocytic Neoplasms - Langerhans Cell Histiocytosis (off -label) (must meet all):

1. Diagnosis of Langerhans Cell Histiocytosis;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years of age;
4. If the request is for first-line or subsequent therapy for RET fusion target for single agent, useful in certain circumstances, for (i, ii, iii, iv, or v):
   i. Multisystem Langerhans Cell Histiocytosis (LCH) with symptomatic or impending organ dysfunction;
   ii. Pulmonary LCH;
   iii. Multifocal single system bone disease not responsive to treatment with a bisphosphonate and >2 lesions (useful in certain circumstances);
   iv. CNS lesions;
   v. Relapsed/refractory disease;
5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 3 months
Medicaid: 3 months

C. Histiocytic Neoplasms- Erdheim-Chester Disease (off -label) (must meet all):

1. Diagnosis of Erdheim-Chester Disease;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years of age;
4. Request is for one of the following (a or b):
   a. As preferred first-line or subsequent therapy for mitogen-activated protein (MAP) kinase pathway mutation;
   b. If the request is for First-line or subsequent therapy for RET fusion target as a single agent (i or ii):
      i. Erdheim-Chester Disease (ECD) with symptomatic disease;
      ii. Relapsed/refractory disease;
5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 3 months
Medicaid: 3 months

D. Histiocytic Neoplasms - Rosai-Dorfman Disease (off -label) (must meet all):

1. Diagnosis of Rosai-Dorfman Disease;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years of age;
4. If the request if for first-line or subsequent therapy for RET fusion target as a single agent (a, b or c):
   a. Symptomatic unresectable (bulky/site of disease) unifocal disease;
   b. Symptomatic multifocal disease;
   c. Relapsed/refractory disease;
5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 3 months
Medicaid: 3 months

Approval Duration
Commercial: 3 months
Medicaid: 3 months

II. Continued Therapy Approval

A. Non-Small Cell Lung Cancer or Medullary Thyroid Cancer and other off label indications (must meet all):

1. Member is currently receiving Retevmo™ as authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. The member is responding positively to therapy;
3. The member is ≥ 12 years of age;
4. Maximum Dose does not exceed (a or b):
   a. 240 mg per day for < 50 kg weight;
   b. 320 mg per day for ≥ 50 kg weight;
5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice

guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval Duration

Commercial: 6 months

Medicaid: 6 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key

ECOG: Eastern Cooperative Oncology Group
NSCLC: Non-Small Cell Lung Cancer
MTC: medullary thyroid cancer
ALT: alanine transaminase
AST: aspartate aminotransferase
TSH: Thyroid stimulating hormone

APPENDIX B: Therapeutic Alternatives

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/Maximum Dose
RET-Positive NSCLC therapies/ RET-Positive Thyroid Cancer and Medullary Thyroid Cancer		
Gavreto	400 mg/day orally	400 mg/day orally

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None Reported.

- Boxed Warning(s):
  - None Reported.

APPENDIX D: General Information

- Hepatotoxicity: 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.
- Severe hepatic impairment (total bilirubin 3.1 to 10 times ULN and any AST).
- Hypertension: Do not initiate Retevmo™ in patients with uncontrolled hypertension. Optimize blood pressure (BP) prior to initiating Retevmo™. Monitor BP after 1 week, at least monthly thereafter and as clinically indicated. Withhold, reduce dose, or permanently discontinue Retevmo™ based on severity.
- QT Interval Prolongation: Monitor patients who are at significant risk of developing QTc prolongation. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment. Monitor 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 severity.

- Hemorrhagic Events: Permanently discontinue Retevmo™ in patients with severe or life-threatening hemorrhage.
- Hypersensitivity: Withhold Retevmo™ and initiate corticosteroids. Upon resolution, resume at a reduced dose and increase dose by 1 dose level each week until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper.
- Tumor Lysis Syndrome: Closely monitor patients at risk 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.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the possible risk to the fetus and to use effective contraception.

References

1. Phase 1/2 Study of LOXO-292 in Patients with Advanced Solid Tumors, RET Fusion-Positive Solid Tumors, and Medullary Thyroid Cancer. Available at: https://clinicaltrials.gov/ct2/show/NCT03157128 . Accessed July 6,2021.
2. Bongarzone I, et al. RET/NTRK1 Rearrangements in Thyroid Gland Tumors of the Papillary Carcinoma Family: Correlation with Clinicopathological Features. Available at: https://pubmed.ncbi.nlm.nih.gov/9516975/ . Accessed July 6,2021.
3. Retevmo™ Prescribing Information. Indianapolis, IN; Lilly: January 2021. Available at: https://uspl.lilly.com/retevmo/retevmo.html#pi . Accessed July 6, 2021.
4. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at: https://www.clinicalkey.com/pharmacology/. Accessed July 6, 2021.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	07/07/2020	09/14/2020
Policy was reviewed: 1. Line of Business was updated from “Commercial, Medicaid” to “All line of Business”. 2. Background was updated to remove “Thyroid cancer is the most common type of endocrine cancer…”. 3. Background was updated to include “This indication is approved under accelerated approval based on overall response rate and duration of response…” 4. Dosing Information dosing regimen was updated to include hepatic impairment dosing “Severe hepatic impairment: Reduce the starting dose to 80 mg orally	07/06/2021	09/14/2021

twice daily regardless of the original starting dose". 5. Dosing Information maximum dose was updated from "160mg orally twice daily; 80mg orally twice daily;" to "<50kg: 240mg/day orally; ≥50kg: 320mg/day orally;". 6. Dosing Information footnote was updated to remove "*Severe hepatic impairment…". 7. Statement about provider sample ''The provision of provider samples does not guarantee coverage…" was added to Clinical Policy. 8. Initial Approval Criteria I.A.5 was updated to include "Maximum Dose does not exceed (a or b)…". 9. Initial Approval Criteria I.A.5.a was updated to include "240 mg per day for < 50 kg weight;". 10. Initial Approval Criteria I.A.5.b was updated to include "320 mg per day for ≥ 50 kg weight;". 11. Initial Approval Criteria I.B was updated to include off-label indication "Histiocytic Neoplasms - Langerhans Cell Histiocytosis (off -label)…". 12. Initial Approval Criteria I.C was updated to include off-label indication "Histiocytic Neoplasms- Erdheim-Chester Disease (off -label)…". 13. Initial Approval Criteria I.D was updated to include off-label indication "Histiocytic Neoplasms - Rosai-Dorfman Disease (off -label)…".		

14. Continued Therapy Approval Criteria II.A was updated from “Non-Small Cell Lung Cancer” to “Non-Small Cell Lung Cancer or Medullary Thyroid Cancer and other off label indications (must meet all)…”. 15. Continued Therapy Criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 16. Continued Therapy Criteria II.A.4 was updated to include “Maximum Dose does not exceed (a or b)…”. 17. Continued Therapy Criteria II.A.4.a was updated to include “240 mg per day for < 50 kg weight;”. 18. Continued Therapy Criteria II.A.4.b was updated to include “320 mg per day for ≥ 50 kg weight;”. 19. Continued Therapy Criteria II.A.5 was updated to include “Dose is within FDA maximum limit for any FDA-approved indication…”. 20. Appendix A was updated to include abbreviations ALT, AST, and TSH. 21. Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance..". 22. Appendix B: Therapeutic Alternatives was updated to combine indications “RET-Positive NSCLC” and “RET-Positive Thyroid Cancer and Medullary Thyroid Cancer” into one category.		

23. Appendix B: Therapeutic Alternatives was updated to remove drug names Alcensa, alectinib, Caprelsa, vandetanib, Cometriq, cabozantinib S-malate, Lenvima, Lenvatinib, Nexavar, sorafenib, Sutent, and sunitinib. 24. Appendix B was updated to remove phrases “RET-Positive NSCLC: Alecensa (alectinib) has been tried, along with Caprelsa (vandetanib) and Cometriq (cabozantinib S-malate). None are FDA-approved for RET NSCLC” and “RET-Positive Thyroid Cancer and Medullary Thyroid Cancer: Caprelsa (vandetanib), Cometriq (cabozantinib Smalate), Lenvima (lenvatinib), and Nexavar (sorafenib) are used. Off label, Sutent (sunitinib) has been used”. 25. Appendix B: Therapeutic Alternatives was updated to include drug name “Gavetro” and its respective dosing regimen and dose limit. 26. Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 27. Appendix D: General Information was updated to include several warnings and		

precautions, "Hepatotoxicity…", "Severe hepatic impairment…", "Hypertension…", "QT Interval Prolongation…", "Hemorrhagic Events…", "Hypersensitivity…", "Tumor Lysis Syndrome…", "Risk of Impaired Wound Healing…", and "Embryo-Fetal Toxicity…". 28. References were reviewed and updated. 29.		