Drug Policy:

Rozlytrek™ (entrectinib)

POLICY NUMBER UM ONC_1367	SUBJECT Rozlytrek™ (entrectinib)		DEPT/PROGRAM UM Dept	PAGE 1 of 4
DATES COMMITTEE REVIEWED 09/11/19, 12/11/19, 04/08/20, 03/10/21, 11/15/21, 03/09/22, 05/11/22, 09/14/22, 07/12/23, 07/10/24	APPROVAL DATE July 10, 2024	EFFECTIVE DATE July 26, 2024	COMMITTEE APPROVAL DATES 09/11/19, 12/11/19, 04/08/20, 03/10/21, 11/15/21, 03/09/22, 05/11/22, 09/14/22, 07/12/23, 07/10/24	
PRIMARY BUSINESS OWNER: UM		COMMITTEE/BOARD APPROVAL Utilization Management Committee		
NCQA STANDARDS UM 2		ADDITIONAL AREAS OF IMPACT		
CMS REQUIREMENTS	STATE/FEDERAL REQUIREMENTS		APPLICABLE LINES OF BUSINESS Commercial, Exchange, Medicaid	

I. PURPOSE

To define and describe the accepted indications for Rozlytrek (entrectinib) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

II. INDICATIONS FOR USE/INCLUSION CRITERIA

A. Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided:

1. The requested medication was used within the last year, AND
2. The member has not experienced disease progression and/or no intolerance to the requested medication, AND
3. Additional medication(s) are not being added to the continuation request.

B. Non-small cell lung cancer (NSCLC)

1. The member has recurrent, advanced, or metastatic NSCLC and Rozlytrek (entrectinib) may be used as a single agent in members with ROS-1 rearrangement-positive NSCLC as first-line or subsequent therapy.

C. NTRK-Fusion Positive Metastatic Solid Tumors

1. Rozlytrek (entrectinib) may be used as a single agent as initial or subsequent therapy in adult and pediatric members older than 1 month of age with recurrent/metastatic/unresectable solid tumors (e.g., NSCLC) with a positive NTRK fusion in the tumor tissue (test confirmation required).

III. EXCLUSION CRITERIA

A. Rozlytrek (entrectinib) is used after disease progression with the same regimen or other NTRK-targeted therapy [e.g.,Vitrakvi (larotrectinib)], unless the member has progressed on first line Rozlytrek (entrectinnib) for ROS-1 rearrangement positive NSCLC. In this setting, Rozlytrek (entrectinnib) may be continued as subsequent therapy if the member is asymptomatic or has disease that is limited to lung cancer with CNS progression as the exception.

B. Concurrent use with other anti-cancer therapies.

C. Dosing exceeds single dose limit of Rozlytrek (entrectinib) 600 mg in Non-Small Cell Lung Cancer.

D. Refer to Tables 1 and 2 below for dosing limits for NTRK-Fusion-Positive Metastatic Solid Tumors.

Table 1. Recommended dosage for Adults and Pediatric patients for the Treatment of *NTRK* Gene Fusion-Positive Solid Tumors

Patient Population	Recommended Dosage of ROZLYTREK	Duration of Treatment
Adults Pediatric patients with BSA ≥ 1.51 m^2:	600 mg orally once daily	Until disease progression or unacceptable toxicity.
Pediatric patients > 6 months:	see Table 2	
Pediatric patients > 1 month to ≤ 6 months:	250 mg/m^2 orally once daily*	

Table 2. Recommended dosage for Pediatric Patients Older than 6 Months for the Treatment of NTRK Gene Fusion-Positive Solid Tumors

Body Surface Area (BSA)*	Recommended Dosage Orally Once Daily
≤0.50 m^2	300 mg/m^2 **
0.51 to 0.80 m^2	200 mg
0.81 to 1.10 m^2	300 mg
1.11 to 1.50 m^2	400 mg
≥ 1.51 m^2	600 mg

E. Treatment exceeds the maximum limit of 180 (100 mg) and 90 (200 mg) tablets/month.

F. Investigational use of Rozlytrek (entrectinib) with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not

supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:

1. Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
2. Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
3. Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definitions of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
4. Whether the experimental design, considering the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).
5. That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
6. That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
7. That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

IV. MEDICATION MANAGEMENT

A. Please refer to the FDA label/package insert for details regarding these topics.

V. APPROVAL AUTHORITY

A. Review – Utilization Management Department

B. Final Approval – Utilization Management Committee

VI. ATTACHMENTS

A. None

VII. REFERENCES

A. Garcia-Foncillas, et al. Indirect Treatment Comparison of Larotrectinib versus Entrectinib in Treating Patients with TRK Gene Fusion Cancers. Cancers 2022, 14, 1793.

B. Desai AV, et al. Entrectinib in children and young adults with solid or primary CNS tumors harboring NTRK, ROS1, or ALK aberrations (STARTRK-NG). Neuro Oncol. 2022 Oct 3;24(10):1776-1789. doi: 10.1093/neuonc/noac087

C. Drilon A, et al. Tumor-agnostic precision immuno-oncology and somatic targeting rationale for you (TAPISTRY): A novel platform umbrella trial. Journal of Clin Onc. 2021 May 28; 39(15). https://doi.org/10.1200/JCO.2021.39.15_suppl.TPS3154

D. Drilon A, et al. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. Lancet Oncol. 2020 Feb;21(2):261-270.

E. Doebele RC, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol. 2020 Feb;21(2):271-282.

F. Rozlytrek prescribing information. Genentech Inc South San Francisco, CA 2024.

G. Clinical Pharmacology Elsevier Gold Standard 2023.

H. Micromedex® Healthcare Series: Micromedex Drugdex Ann Arbor, Michigan 2023.

I. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2023.

J. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD 2023.

K. Ellis LM, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014 Apr 20;32(12):1277-80.

L. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf.