repotrectinib (Augtyro™)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO304

Description

Repotrectinib (Augtyro) is an orally administered selective tyrosine kinase inhibitor (TKI).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
repotrectinib (Augtyro)	Advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC) Neurotrophic receptor tyrosine kinase (NTRK) gene fusion positive solid tumors	40 mg capsules	240 capsules/30 days
		160 mg capsules	60 capsules/30 days

Initial Evaluation

I. **Repotrectinib (Augtyro)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   B. Medication is not used in combination with any other oncology therapy; **AND**
   C. A diagnosis of one of the following:
      1. **Non-small cell lung cancer (NSCLC); AND**
         i. Member is 18 years of age or older; **AND**
         ii. Confirmation of ROS1-postive mutation; **AND**
         iii. The disease is advanced (Stage III); **OR**
         iv. The disease is metastatic (IV); **AND**
            a. There is no evident CNS metastases; **AND**
               i. Treatment with entrectinib (Rozlytrek) or crizotinib (Xalkori) have been ineffective, contraindicated, or not tolerated; **OR**
            b. There is CNS metastases; **AND**
               i. Treatment with entrectinib (Rozlytrek) has been ineffective, contraindicated, or not tolerated; **OR**
      2. **Solid tumor; AND**
         i. Member is 12 years of age or older; **AND**
         ii. The disease is advanced (stage III), metastatic (stage IV), or unresectable; **AND**

iii. Confirmation of neurotrophic receptor tyrosine kinase (NTRK) gene fusion; **AND**
iv. Documentation of intolerance or contraindication to entrectinib (Rozlytrek)
v. Provider attestation that all alternative therapies for diagnosis and stage of cancer per compendia have been exhausted, as defined by:
   a. Progression following all appropriate treatments; **OR**
   b. Nonresponse to all available therapies; **OR**
   c. All available therapies are contraindicated or not tolerated; **OR**
   d. No standard or satisfactory treatment exist

II. Repotrectinib (Augtyro) is considered investigational when used for all other conditions, including but not limited to:
   A. NSCLC with other mutations (e.g. ALK, RET, BRAF, etc.)
   B. Solid tumors with ROS1 rearrangement
   C. Repotrectinib (Augtyro) used in combination with another oncology therapy
   D. KRAS-mutant solid tumors

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise; **AND**
III. Member has exhibited response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
IV. Medication is not used in combination with any other oncology therapy

Supporting Evidence

I. Repotrectinib (Augtyro) is a ROS1 tyrosine kinase inhibitor (TKI), FDA-approved for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC) and neurotrophic receptor tyrosine kinase (NTRK) gene fusion positive solid tumors. Repotrectinib (Augtyro) is an oral capsule administered once daily for 14 days, then increased to twice daily thereafter.

Non-small cell lung cancer (NSCLC)

II. Lung cancer is the second most common cancer diagnosed in the United States and the leading cause of cancer-related death. Non-small cell lung cancer represents up to 85% of lung cancer diagnoses. ROS1 fusions are rare and occur in about 1-2% of patients with NSCLC. The median age of diagnosis is 50 years old and ROS1 rearrangement is more common in females. ROS1 rearrangement tends to be more aggressive and there is an increased risk of G2032R mutations, which result in TKI resistance, and ultimately, fewer treatment options. Central nervous system metastases are the most common site of disease progression after development of TKI

resistance. Given the complexity of management of mCRC, the treatment of mCRC must be initiated by, in or consultation with an oncologist.

III. Repotrectinib (Augtyro) is the third FDA-approved TKI and joins entrectinib (Rozlytrek) and crizotinib (Xalkori) for treatment of ROS1-positive NSCLC. Repotrectinib (Augtyro) is the first TKI approval that includes patients with ROS1-positive non-small cell lung cancer who have previously received a ROS1 tyrosine kinase inhibitor, in addition to patients who are tyrosine kinase inhibitor naïve. Repotrectinib (Augtyro) will compete against entrectinib (Rozlytrek) and crizotinib (Xalkori) in the first- and second-line setting.

IV. Repotrectinib (Augtyro) was studied in a Phase 1/2, international, multicenter, single arm, open label, multi cohort study which included 71 TKI-naïve participants who received up to one prior line of platinum-based chemotherapy and 56 participants who received 1 prior ROS1 TKI with no prior platinum-based chemotherapy. Participants received repotrectinib (Augtyro) 160mg once daily for 12 days, then 160mg twice daily. Baseline characteristics were similar between both cohorts: median age 57 years old, mostly female (>60%), of those ROS1 TKI-naïve, 72% of participants were also chemotherapy naïve, there was 24% brain metastases in the TKI-naïve group and 46% in the prior TKI group, and of those that had prior TKI therapy, 82% had received crizotinib. The primary endpoint, overall response rate (ORR), was 78% (n=56, 95% CI, 68-88) for the TKI-naïve cohort and 38% (n=56, 95% CI, 25-52) for the cohort with prior TKI. The median progression free survival (PFS) was 35.7 months (95% CI, 27.4-non-estimable) and 9.0 months (95%, 17.8-non-estimable) for the TKI-naïve and prior TKI cohorts, respectively. The median time to response was 1.8 months.

V. The safety analysis was completed in all 426 participants of the Phase 2 pooled population, which included other genetic mutations (e.g. ALK, NTRK1-3, etc.). The most common adverse events included dizziness (58%), dysgeusia (50%), paresthesia (30%), constipation (26%), anemia (26%), and ataxia (20%). Adverse events led to dose reduction in 163 participants (38%), dose interruption in 213 participants (50%), and treatment discontinuation in 31 participants (7%).

VI. There is moderate confidence that repotrectinib (Augtyro) provides an objective and meaningful difference in patients with NSCLC. Although there is low confidence in the single arm, open label study design, the trial has a similar study design and comparable efficacy endpoints to similar treatment options. Repotrectinib's (Augtyro) efficacy endpoints are promising as the duration of response and progression free survival are non-estimable and quality of life measures demonstrate an increase of ≥ 10 points at cycle 6 and stable scores throughout treatment.

VII. The National Comprehensive Cancer Network (NCCN) guidelines have been updated to recommend entrectinib (Rozlytrek), crizotinib (Xalkori), and repotrectinib (Augtyro) as first and second line therapy for NSCLC with ROS1 fusion (category 2A, all preferred). After progression on therapy, if there is brain metastases, guidelines recommend entrectinib (Rozlytrek), repotrectinib (Augtyro), or lorlatinib (Lobrena) (category 2A). The TRIDENT-1 trial permitted participants to receive prior entrectinib (Rozlytrek) (N= 9, 16%) or crizotinib (Xalkori) (N= 46, 82%) and requiring step through these agents for metastatic disease is both clinically appropriate and cost-effective.

Solid tumor with a confirmed neurotrophic receptor tyrosine kinase (NTRK) gene fusion

VIII. Neurotrophic tropomyosin kinase (NTRK) receptors are part of the transmembrane tyrosine kinases responsible for neuronal development. Although NTRK gene fusion is present in both adult and pediatric populations, it is less prevalent (<5%) in common tumor types like colorectal, breast, and lung adenocarcinomas. NTRK gene fusion is most prevalent (>90%) in rare forms of tumors, such as head and neck cancers (e.g., secretory mammary carcinoma and mammary analogue secretory carcinoma (MASC)), and rare forms of soft tissue sarcomas. Due to the rarity of NTRK gene fusion positive tumors, confirmation laboratories testing is required for diagnosis.

IX. Repotrectinib (Augtyro) is the third FDA-approved TKI and joins entrectinib (Rozlytrek) and larotrectinib (Vitrakvi) for the treatment of NTRK gene fusion positive solid tumors that are locally advanced or metastatic or unresectable.

X. Repotrectinib (Augtyro) was approved for treatment in NTRK gene fusion positive solid tumors under the accelerated pathway. Repotrectinib (Augtyro) was studied in a Phase 2, multicenter, single-arm, open-label, cohort expansion study (TRIDENT-1) in the setting of NTRK gene fusion positive tumors. The multi-cohort trial included 40 TKI-naïve participants and 48 TKI-pretreated participants. TKI-pretreated participants received up to two prior TKI therapies (e.g. entrectinib, larotrectinib, selitrectinib, or cabozantinib). Participants received repotrectinib (Augtyro) 160 mg once daily for 14 days, then 160 mg twice daily. The TKI-pretreated cohort had a higher proportion of participants who had at least one prior chemotherapy or immunotherapy systemic treatment regimen compared to the TKI-naïve cohort. The median age of participants was 61 years old in TKI-naïve cohort and 58 years old in the TKI-pretreated cohort. The proportion of Asian participants in TKI-naïve cohort was 53% and the proportion of White participants in TKI-pretreated cohort was 65%. The primary endpoint, overall response rate (ORR), was 58% (n=40, 95% CI, 41-73) for TKI-naïve cohort and 50% (n=48, 95% CI, 35-65) for TKI-pretreated cohort. The median duration of response (DOR) was not estimable in TKI-naïve cohort and 9.9 months (95% 7.4-13) for TKI-pretreated cohort.

XI. The safety analysis for NTRK gene fusion positive solid tumors was completed in all 426 participants of the Phase 2 (TRIDENT-1) pooled population, which included other genetic mutations (e.g. ALK, ROS1-positive NSCLC, etc.). The most common adverse events included dizziness (58%), dysgeusia (50%), paresthesia (30%), constipation (26%), anemia (26%), and ataxia (20%). Adverse events led to dose reduction in 163 participants (38%), dose interruption in 213 participants (50%), and treatment discontinuation in 31 participants (7%).

XII. Despite statistically significant outcomes, there are concerns with the use of surrogate primary and secondary endpoints, as they do not translate to clinical outcomes and a lack of a placebo or comparator arm to demonstrate true clinical effect. There is low confidence that repotrectinib (Augtyro) provides a clinically objective and meaningful difference in patients with NTRK positive solid tumors.

XIII. The NCCN guidelines recommend different treatment options dependent on tumor type. For example, salivary gland cancers are among the most common solid tumors with NTRK fusion. In salivary gland cancers with NTRK fusion, NCCN recommends laratrectinib (Vitrakvi), entrectinib (Rozlytrek), and repotrectinib (Augtyro) (Category 2 recommendation) whereas the treatment recommendation is different for soft tissue cancers. The TRIDENT-1 trial permitted participants to receive prior entrectinib (Rozlytrek) prior to randomization and repotrectinib (Augtyro) is

recommended as subsequent second line therapy after treatment with prior TKI (category 2a recommendation). Therefore, requiring step through these agents for metastatic disease is both clinically appropriate and cost-effective.

Investigational or Not Medically Necessary Uses

I. There are ongoing clinical studies to assess efficacy and safety of repotrectinib (Augtyro) in other settings. Notably, clinical trials in the settings of NSCLC with other mutations are underway. Repotrectinib (Augtyro) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. NSCLC with other mutations (e.g. ALK, RET, BRAF, etc.)
   B. Solid tumors with ROS1 rearrangement
   C. Repotrectinib (Augtyro) used in combination with another oncology therapy
   D. KRAS-mutant solid tumors

References

1. Augtyro (repotrectinib) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; November 2023.
2. Drilon A, Camidge DR, Lin JJ, et al. Repotrectinib in ROS1 Fusion-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2024;390(2):118-131.
3. Food and Drug Administration. FDA approves repotrectinib for ROS1-positive non-small cell lung cancer. Updated November 11, 2023. Accessed January 30, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-repotrectinib-ros1-positive-non-small-cell-lung-cancer.
4. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Versions 2.2024 – February 9, 2024). 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 17, 2024.
5. Westphalen CB, Krebs MG, Le Tourneau C, et al. Genomic context of NTRK1/2/3 fusion-positive tumours from a large real-world population. Npj Precis Oncol. 2021;5(1):1-9. doi:10.1038/s41698-021-00206-y
6. Manea CA, Badiu DC, Ploscaru IC, et al. A review of NTRK fusions in cancer. Ann Med Surg. 2022;79:103893. doi:10.1016/j.amsu.2022.103893

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
entrectinib (Rozlytrek®)	Neurotrophic receptor tyrosine kinase gene fusion positive solid tumors
	NSCLC, metastatic, ROS1-positive
ALK+ Inhibitors	NSCLC, metastatic, ALK-positive
	NSCLC, metastatic, ROS1- positive
	Recurrent, refractory, Inflammatory myofibroblastic tumors, ALK-positive, unresectable
	Relapsed, refractory systemic anaplastic large cell lymphoma, ALK-positive
encorafenib (Braftovi®), binimetinib (Mektovi®)	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therap

	Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy
pralsetinib (Gavreto®)	RET Fusion-Positive Non-Small Cell Lung Cancer
sotorasib (Lumakras®)	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with a KRAS G12C mutation

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated to include new indication for NTRK positive solid tumors in patients 12 years and older and new initial evaluation criteria. Addition of new strength formulation and quantity limit. Addition of new E/I indication. Updated supporting evidence.	02/2025
Policy created	05/2024