taletrectinib (Ibtrozi™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO332

Description

Taletrectinib (Ibtrozi) is an orally administered ROS1 selective tyrosine kinase inhibitor (TKI).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
taletrectinib (Ibtrozi)	Advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC)	200mg capsules	90 capsules/30 days

Initial Evaluation

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

*Please note: medications notated with an asterisk may require additional review.

II. Taletrectinib (Ibtrozi) 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. CDH1-mutated breast cancer
   D. Taletrectinib (Ibtrozi) used in combination with another oncology therapy

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 will not be used in combination with any other oncology therapy

Supporting Evidence

I. Taletrectinib (Ibtrozi) 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). Taletrectinib (Ibtrozi) is a once daily orally administered capsule and it is the fourth FDA-approved TKI joining repotrectinib (Augtyro), entrectinib (Rozlytrek), and crizotinib (Xalkori) for treatment of ROS1-positive NSCLC. Taletrectinib (Ibtrozi) will compete against repotrectinib (Augtyro), entrectinib (Rozlytrek), and crizotinib (Xalkori) in the first- and second-line setting.
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. The ROS1 fusions is rare and occur in about 1-2% of patients with NSCLC. The median age of diagnosis is 50 years and ROS1 rearrangement is more common in females. The 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. Taletrectinib (Ibtrozi) was studied in clinical trials for ROS1+ NSCLC as monotherapy. Appropriate washout periods of chemotherapy were required for consideration under inclusion criteria. At this time, there is insufficient evidence to support the efficacy and safety of ROS1 selective TKI's used in combination with other oncology therapies.
IV. Taletrectinib (Ibtrozi) was studied two Phase 2, open-label, single-arm, non-randomized (TRUST I/II) studies, which included 160 TKI-naïve participants and 113 participants who received one prior ROS1 TKI. Participants received taletrectinib (Ibtrozi) 600mg once daily in 21-day treatment cycles until disease progression or unacceptable toxicity. Baseline characteristics were similar between both cohorts: median age 56 years old, mostly female (57%), stage IV disease (94%), and chemotherapy-naïve regardless of prior TKI treatment (73%). Of the participants who have received previous TKI therapy, most were previously treated with crizotinib (Xalcori) (91%), while the remaining 9% were previously treated with entrectinib (Rozlytrek).The primary endpoint, overall response rate (ORR), was 88.8% (n=142, 95% CI, 82.8-93.2) for the TKI-naïve

cohort and 55.8% (n=63, 95% CI, 46.1-65.1) for the cohort with prior TKI. The median progression free survival (PFS) was 45.6 months (95% CI, 29.0-non-estimable) and 9.7 months (95%, 9.7-non-estimable) for the TKI-naïve and prior TKI cohorts, respectively. The median time to response was 1.4 months in both cohorts. There is low confidence that taletrectinib (Ibtrozi) provides a clinically objective and meaningful difference in patients with ROS1 NSCLC. The single arm, open label study design is of low quality, and creates probability of selection and assessment biases. Overall response rate (ORR) is a surrogate marker and does not correlate with clinically significant outcomes, such as effects on morbidity or mortality. Therefore, uncertainty lies in the validity of results and/or applicability to patients. Confirmation of benefit is required from a Phase 3, randomized controlled trial.

V. The safety analysis was completed in all 352 participants of the TRUST I/II pooled population, which included patients with ROS1 NSCLC and other solid tumors. The most common adverse events included elevated AST (72%), elevated ALT (68%), diarrhea (64%), nausea (46%), dizziness (21%), and vomiting (44%). Adverse events led to a dose reduction in 102 participants (29%), dose interruption in 143 participants (40.6%), and treatment discontinuation in 23 participants (6.5%).

VI. The National Comprehensive Cancer Network (NCCN) guidelines have been updated to recommend entrectinib (Rozlytrek), crizotinib (Xalkori), repotrectinib (Augtyro), and taletrectinib (Ibtrozi) as first and second line therapy (category 2A, all preferred) for locally advanced and metastatic (stage III-IV) ROS1 NSCLC. The pooled TRUST I/II studies permitted participants to receive prior entrectinib (Rozlytrek) (N= 10, 8.8%) or crizotinib (Xalkori) (N= 103, 91.2%). Requiring step through these agents is both clinically appropriate and cost-effective. Indirect safety profile comparisons suggest that taletrectinib (Ibtrozi) demonstrated lower rates of neurological adverse effects (e.g., dizziness, ataxia, etc.) compared to that of other TKI's in this disease space. However, as of August 2025, there are currently no published head-head trials comparing the safety and efficacy of ROS1 TKIs. The clinical meaningfulness and safety of these differences remain unknown.

VII. After progression on therapy, if there is metastasis to the brain, NCCN recommends repotrectinib (Augtyro), taletrectinib (Ibtrozi), lorlatinib (Lobrena), or entrectinib (Rozlytrek) (category 2A). Of the response-evaluable population (REP) in the TRUST I/II pooled studies, 33.7% (n=92) participants had brain metastasis at baseline, with 17.9% (n=49) with metastasizes that were measurable. Intracranial overall response rate (cORR) was 76.5% (n=13, 95% CI, 63.6-98.5) for the TKI-naïve cohort and 65.5% (n=21, CI 95%, 46.8-81.4) for the TKI previously treated cohort. The TKI previously treated cohort included participants with prior progression on entrectinib (Rozlytrek). Therefore, requiring step through entrectinib (Rozlytrek) 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 taletrectinib (Ibtrozi) in other settings. Taletrectinib (Ibtrozi) 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.)**

i. There is currently a lack of scientific studies evaluating the safety and efficacy of taletrectinib (Ibtrozi) in NSCLC mutations outside of ROS1. Thus, there is a lack of scientific evidence to support the treatment of NSCLC mutations outside of ROS1.

B. **Solid tumors with ROS1 rearrangement**

i. ROS1 mutations have been observed in solid tumors (i.g. pancreatic cancers hepatoma, breast cancer, sarcoma), however there is currently a lack of scientific studies evaluating the safety and efficacy of taletrectinib (Ibtrozi) outside of the NSCLC space. There is a lack of scientific evidence to support the treatment of solid tumors with ROS1 rearrangement.

C. **CDH1-mutated breast cancer**

i. A phase II study of taletrectinib (Ibtrozi) in previously treated metastatic CDH1-mutated Invasive Lobular Cancer (ILC) of the breast (TaCe) has been suspended as of May 2025. No results have been posted. The safety and efficacy of taletrectinib (Ibtrozi) used in the setting of ILC and/or breast cancer is not adequately supported.

D. **Taletrectinib (Ibtrozi) used in combination with another oncology therapy**

i. Taletrectinib (Ibtrozi) is FDA-approved for monotherapy in the setting of ROS1 NSCLC. NCCN guidelines also recommend use of taletrectinib (Ibtrozi) as monotherapy. There is currently a lack of scientific studies evaluating the safety and efficacy of taletrectinib (Ibtrozi) in combination with other oncology therapy.

References

1. Ibtrozi (taletrectinib) [prescribing information]. Burlington, MA: Nuvation Bio Inc.; June 2025.
2. Pérol, Maurice et al. Taletrectinib in *ROS1*+ Non-Small Cell Lung Cancer: TRUST. *Journal of clinical oncology*. *official journal of the American Society of Clinical Oncology*. 2025;43(16): 1920-1929.
3. Food and Drug Administration. FDA approves taletrectinib for ROS1-positive non-small cell lung cancer. Updated June 11, 2025. Accessed July 16, 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-taletrectinib-ros1-positive-non-small-cell-lung-cancer
4. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Versions 5.2025 – June 20, 2025). 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 30, 2025.

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
repotrectinib (Augtyro™)	Advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC)
	Neurotrophic receptor tyrosine kinase (NTRK) gene fusion positive solid tumors
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

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2025