

Repotrectinib (AUGTYRO) National Drug Mini-Monograph June 2026

VA Pharmacy Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: AC, active-controlled; CO, crossover; DB, double-blind; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MC, multicenter; MN, multinational; PC, placebo-controlled; Q, GRADE quality of evidence; RCT, randomized clinical trial

FDA PRESCRIBING INFORMATION

Description / MOA	Repotrectinib is an inhibitor of proto-oncogene tyrosine-protein kinase ROS1 (ROS1) and of the tropomyosin receptor tyrosine kinases (TRKs) TRKA, TRKB, and TRKC. Fusion proteins of ROS1 or TRK cause downstream signaling pathways leading to cell proliferation.
Indication Under Review	<ul style="list-style-type: none"> Locally advanced or metastatic ROS-1 fusion positive non-small cell lung cancer Patients with a solid tumor with a neurotrophic tyrosine receptor kinase (NTRK) gene fusion with locally advanced or metastatic disease where surgery would cause morbidity and progressed following treatment or have non satisfactory alternative therapy.
Dosage Regimen	160mg capsules orally daily for 14 days, then increase to twice a day
Dosage Forms Under Review	40 and 160mg capsules
Pretreatment Procedures	☐ Serum uric acid

EFFICACY CONSIDERATIONS

Trial 1	TRIDENT-1 (ROS1-positive NSCLC cohort) phase 1-2 ¹			
Design	Multicenter, single-arm, open-label, multi-cohort clinical trial			
Population	Adult and pediatric patients (≥12 years) with locally advanced or metastatic ROS1-positive NSCLC and an ECOG performance status ≤1.			
Intervention	Repotrectinib 160 mg orally once daily for 14 days, followed by 160 mg twice daily			
Comparator	None (single-arm).			
Results				
	Outcome	ROS1 TKI Naïve	1 prior ROS1 TKI	RR (95% CI)
	ORR by BICR	79%	38%	
	mDOR	34.1 months	14.8 mos	
	mPFS	35.7 mos	9.0 mos	
	Intracranial ORR (baseline disease)	89%	38%	
	Intracranial PFS at 12 months (no baseline disease)	91%	82%	
	ORR=Objective Response Rate; DOR=Duration of Response; PFS=progression-free survival;			
Authors' Conclusions	Repotrectinib demonstrated durable clinical activity in patients with ROS1-positive NSCLC, regardless of prior TKI treatment, with intracranial activity.			
Trial 2	TRIDENT-1 (NTRK-positive solid tumor cohort) ²			
Design	Multicenter, single-arm, open-label, multi-cohort clinical trial.			
Population	Adult and pediatric patients (≥12 years) with locally advanced or metastatic solid tumors harboring an NTRK gene fusion and ECOG performance status ≤1			
Intervention	Repotrectinib 160 mg orally once daily for 14 days, followed by 160 mg twice daily.			
Comparator	None (single-arm)			

Results	Outcome	TRK TKI Naive	Prior TRK TKI	RR (95% CI)
	ORR by BICR	59%	48%	
	mDOR	NR	9.8 months	
	mPFS	30.3 months	7.4 months	
	Intracranial ORR (baseline disease)	67%	67%	
	Intracranial PFS at 24 mos (no baseline disease)	87%	67%	
ORR=Objective Response Rate; DOR=Duration of Response; PFS=progression-free survival;				
Authors' Conclusions	Repotrectinib showed durable systemic and intracranial activity across multiple tumor types and NTRK fusion partners, including in TKI-pretreated patients with resistance mutations.			
NCCN Guidelines	ROS1 Gene Fusion in NSCLC Preferred 1 st line: Crizotinib or Entrectinib or Repotrectinib or Taletrectinib NTRK Gene Fusion in Solid Tumors Preferred 1 st line: Entrectinib or Larotrectinib or Repotrectinib			
VA Clinical Pathway	Current ROS1 Gene Fusion NSCLC: Entrectinib NTRK Gene Fusion NSCLC: Entrectinib			

SAFETY CONSIDERATIONS³

Boxed Warnings	None
Contraindications	None
Other Warnings	Central nervous system (CNS) adverse reactions occurred in 77% of patients, including dizziness (65%), ataxia (28%), and cognitive impairment (25%). Interstitial lung disease (ILD)/pneumonitis occurred in 3.1%. Hepatotoxicity was observed, with increased ALT in 38% and AST in 41%. Myalgia occurred in 13% of patients, sometimes with CPK elevation. Hyperuricemia was reported in 5%. Skeletal fractures occurred in 2.3% of adult patients.
Top 5 AEs	1. Dizziness (65%), Dysgeusia (54%), 3. Peripheral neuropathy (49%), 4. Constipation (38%), 5. Fatigue (30%)
Drug Interactions	Avoid concomitant use with strong or moderate CYP3A inhibitors, P-gp inhibitors, and strong or moderate CYP3A inducers. repotrectinib is a CYP3A4 inducer and can reduce the efficacy of CYP3A4 substrates. Avoid concomitant use with hormonal contraceptives.
Pregnancy	Repotrectinib can cause fetal harm
Lactation	Advise lactating women to discontinue breastfeeding during treatment and for 10 days after the last dose.
Trial Safety Results	In the pooled safety population (N=426), Grade 3 or 4 adverse reactions occurred in 45% of patients. Serious adverse reactions occurred in 35%, with pneumonia (6.3%), dyspnea (3.1%), and pleural effusion (2.8%) being the most common. Permanent discontinuation due to adverse reactions occurred in 7% of patients

THERAPEUTIC ALTERNATIVES AND THEIR PLACE IN THERAPY

DRUG	VANF	CFU	FDA	VA Clinical Pathways
Crizotinib	PA-F	Yes	Metastatic NSCLC and ALK or ROS1 positive	None
Entrectinib	PA-F	Yes	Metastatic NSCLC and ROS1 positive Metastatic solid tumor and NTRK -fusion positive no alternative/after tx	Biliary-2 nd Line NTRK Fusion NSCLC-1 st Line ROS1 or NTRK positive Pancreatic-2 nd Line NTRK positive Salivary Gland-R/Metastatic NTRK positive GIST-R/metastatic NTRK positive
Taletrectinib	NF	No	Locally advanced/metastatic NSCLC and ROS1 positive	None
Larotrectinib	NF	Yes	Metastatic solid tumor and NTRK -fusion positive no alternative/after tx	None

POTENTIAL PLACE IN THERAPY OF Repotrectinib

1. Repotrectinib is a kinase inhibitor of ROS1 and TRK, involved in fusions in some non-small cell lung cancers. It has some activity in previously treated disease.
2. Repotrectinib has 2 FDA indications:
 - a. Locally advanced or metastatic ROS1 fusion-positive non-small cell lung cancer (NSCLC)
 - b. Locally advanced or metastatic solid tumors with a NTRK gene fusion where surgery would cause morbidity or if they progressed following treatment or there is no satisfactory alternative treatment
3. In advanced **ROS1 fusion-positive NSCLC**, there are multiple TKIs with FDA indication for ROS1 fusion positive NSCLC. Next generation TKIs, including repotrectinib and taletrectinib, offer improved Progression-Free Survival, better CNS penetration, and activity against resistance mutations compared to first generation TKIs like crizotinib and entrectinib. Although repotrectinib and taletrectinib have good CNS penetration, taletrectinib has lower rates of CNS adverse events but higher rates of GI and transaminase elevation.
4. In advanced **NTRK-fusion positive** solid tumors, there are multiple TKIs with FDA indication for advanced NTRK fusion positive solid tumors in a tumor agnostic approach. Repotrectinib has the least mature data, while larotrectinib has the most mature long-term reported data with a more favorable safety profile.
5. Currently, entrectinib is listed on VA Oncology Clinical Pathway for Lung Cancer for patients with ROS1 fusion positive NSCLC and NTRK fusion positive NSCLC.
6. Consider taletrectinib for advanced ROS1 fusion positive NSCLC and larotrectinib for NTRK fusion positive solid tumors (NSCLC).

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References

¹ Drilon A, et al. Repotrectinib in ROS1 fusion-positive non-small cell lung cancer. *New Eng J Med* 2024; 390: 118-31.

² Besse B, et al. Repotrectinib in NTRK fusion-positive advanced solid tumors: a phase 1/2 trial. *Nat Med* 2026; 32: 682-698.

³ AUGTYRO (repotrectinib) Package Insert. Bristol-Myers Squibb Company. Princeton, NJ. 2024