PDL DRUG REVIEW

Proprietary Name: Augtyro®
Common Name: repotrectinib
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Rozlytrek	Non-Recommended with Conditions
Xalkori	Non-Recommended with Conditions
Zykadia	Non-Recommended with Conditions

Pharmacology/Usage: Repotrectinib, the active ingredient of Augtyro®, is a kinase inhibitor. It is an inhibitor of proto-oncogene tyrosine-protein kinase ROS1 (ROS1) and of the tropomyosin receptor tyrosine kinases (TRKs) TRKA, TRKB, and TRKC.

Indication: For the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC).

There is no pregnancy category for this medication; however, the risk summary indicates that based on literature reports in humans with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action, Augtyro® can cause fetal harm when administered to a pregnant woman. There are no available data on use in pregnant women. Advise pregnant women of the potential risk to a fetus. Verify the pregnancy status of females of childbearing potential prior to starting Augtyro®. Advise females of childbearing potential to use effective non-hormonal contraception during treatment with Augtyro® and for 2 months following the last dose. Advise male patients with female partners of childbearing potential to use effective contraception during treatment and for 4 months following the last dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Capsules: 40mg.

Swallow capsules whole. Do not open, chew, crush, or dissolve prior to swallowing.

Recommended Dosage: Select patients for the treatment of locally advanced or metastatic NSCLC with Augtyro® based on the presence of *ROS1* rearrangement(s) in tumor specimens. An FDA-approved test to detect *ROS1* rearrangements for selecting patients for treatment with Augtyro® is not currently available.

Prior to initiating Augtyro®, discontinue strong and moderate CYP3A inhibitors for 3 to 5 elimination half-lives of the CYP3A inhibitor.

Prior to initiation of Augtyro®, assess:

- Liver function tests, including bilirubin.
- Uric acid level.

The recommended dosage is 160mg PO QD with or without food for 14 days, then increase to 160mg BID and continue until disease progression or unacceptable toxicity. Take at about the same time each day. If a dose is missed

or if vomiting occurs at any time after taking a dose, skip the dose and resume Augtyro® at its regularly scheduled time.

No dosage modification is recommended for patients with mild or moderate renal impairment; however, the recommended dosage has not been established in patients with severe renal impairment or kidney failure. No dosage modification is recommended with mild hepatic impairment; however, the recommended dosage of Augtyro® has not been established in patients with moderate or severe hepatic impairment.

Refer to the prescribing information for the recommended dosage modifications of Augtyro® for the management of adverse reactions, such as CNS effects, interstitial lung disease (ILD)/pneumonitis, hepatotoxicity, creatine phosphokinase, hyperuricemia, and other clinically relevant adverse reactions.

Drug Interactions: Avoid concomitant use with strong or moderate CYP3A inhibitors. Concomitant use of Augtyro® with a strong or a moderate CYP3A inhibitor may increase repotrectinib exposure, which may increase the incidence and severity of adverse reactions of Augtyro®. Discontinue CYP3A inhibitors for 3 to 5 elimination half-lives of the CYP3A inhibitor prior to starting Augtyro®.

Avoid concomitant use with P-gp inhibitors. Concomitant use of Augtyro® with a P-gp inhibitor may increase repotrectinib exposure, which may increase the incidence and severity of adverse reactions of Augtyro®.

Avoid concomitant use with strong or moderate CYP3A inducers. Concomitant use of Augtyro® with a strong or moderate CYP3A inducer may decrease repotrectinib plasma concentrations, which may decrease efficacy of Augtyro®.

Repotrectinib is a CYP3A4 inducer. Concomitant use of repotrectinib deceases the concentration of CYP3A4 substrates, which can reduce the efficacy of these substrates. Avoid concomitant use unless otherwise recommended in the prescribing information for CYP3A substrates, where minimal concentration changes can cause reduced efficacy. If concomitant use is unavoidable, increase the CYP3A4 substrate dosage in accordance with approved product labeling.

Repotrectinib is a CYP3A4 inducer, which can decrease progestin or estrogen exposure to an extent that could reduce the effectiveness of hormonal contraceptives. Avoid concomitant use of Augtyro® with hormonal contraceptives. Advise females to use an effective non-hormonal contraceptive.

Box Warning: There is no box warning with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Augtyro®) for all grades. There was no placebo data in the prescribing information to compare with.* The most frequently reported adverse events included dizziness (63%), dysgeusia (48%), peripheral neuropathy (47%), ataxia (28%), cognitive disorders (23%), headache (19%), constipation (36%), nausea (19%), diarrhea (13%), vomiting (10%), dyspnea (30%), cough (14%), fatigue (24%), edema (12%), muscular weakness (21%), myalgia (12%), vision disorders (11%), and increased weight (14%).

Laboratory abnormalities for all grades included decreased hemoglobin (73%), decreased lymphocytes (43%), decreased leukocytes (36%), decreased neutrophils (34%), increased aPTT (25%), increased INR (20%), increased creatine phosphokinase (57%), increased GGT (48%), increased AST (40%), increased ALT (34%), increased sodium (29%), increased alkaline phosphatase (26%), increased glucose (23%), increased urate (21%), and decreased glucose (21%).

Augtyro® can cause CNS adverse reactions. Among patients who received Augtyro® (N=351) in Study TRIDENT-1, a broad spectrum of CNS adverse reactions including dizziness, ataxia, and cognitive disorders occurred in 75% with Grade 3 or 4 events occurring in 4% of patients. Mood disorders occurred in 6%, and sleep disorders (including insomnia and hypersomnia) occurred in 15% of patients. Advise patients and caregivers of the risk of CNS adverse reactions with Augtyro®. In addition, advise patients not to drive or use machines if they are experiencing CNS adverse reactions. Withhold and then resume at the same or reduced dose upon improvement, or permanently discontinue Augtyro® based on severity.

Augtyro® can cause interstitial lung disease (ILD)/pneumonitis. Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold Augtyro® in patients with suspected ILD/pneumonitis and permanently discontinue Augtyro® if ILD/pneumonitis is confirmed.

Augtyro® can cause hepatotoxicity. Monitor liver function tests, including ALT, AST, and bilirubin, every 2 weeks during the first month of treatment, then monthly thereafter and as clinically indicated. Withhold and then resume at the same or reduced dose upon improvement, or permanently discontinue Augtyro® based on the severity.

Augtyro® can cause myalgia with or without creatine phosphokinase (CPK) elevation. Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor serum CPK levels during Augtyro® treatment and monitor CPK levels every 2 weeks during the first month of treatment and as needed in patients reporting unexplained muscle pain, tenderness, or weakness. Initiate supportive care as clinically indicated. Based on severity, withhold and then resume Augtyro® at the same or reduced dose upon improvement.

Augtyro® can cause hyperuricemia. Monitor serum uric acid levels prior to starting Augtyro® and periodically during treatment. Start treatment with urate-lowering medications as clinically indicated. Withhold and then resume at the same or reduced dose upon improvement, or permanently discontinue Augtyro® based on severity.

Augtyro® can cause skeletal fractures. The median time to fracture was 71 days. Promptly assess patients with signs or symptoms of fractures. There are no data on the effects of Augtyro® on healing of known fractures and risk of future fractures.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Bristol-Myers Squibb Company

Analysis: The efficacy of Augtyro® was assessed in a multicenter, single-arm, open-label, multi-cohort clinical trial (TRIDENT-1) that included patients required to have *ROS1*-positive locally advanced or metastatic NSCLC, Eastern Cooperative Oncology Group (ECOG) performance status ≤1, and measurable disease per RECIST v1.1. All were assessed for CNS lesions at baseline, and patients with symptomatic brain metastases were excluded from the trial. Patients received Augtyro® 160mg PO QD X14 days, then increased to 160mg BID until disease progression or unacceptable toxicity. Tumor assessments were performed at least every 8 weeks. The efficacy populations included ROS1 tyrosine kinase inhibitor (TKI)-naïve patients who received up to 1 prior line of platinum-based chemotherapy and/or immunotherapy (N=71) and patients who received 1 prior ROS1 TKI with no prior platinum-based chemotherapy or immunotherapy (N=56).

Of the 71 ROS1 TKI-naïve patients, the median age was 57 years (range 28 to 80), while 60.6% were female, 67.6% were Asian, 63.4% had never smoked, and 66.2% had ECOG performance status of 1 at baseline. At baseline, 94.4% had metastatic disease, 25.4% had CNS metastases by blinded independent central review (BICR), 97.2% had adenocarcinoma, and 28.2% had prior chemotherapy consisting of platinum-based chemotherapy and/or immunotherapy for locally advanced or metastatic disease.

Among the 56 patients who had received 1 prior ROS1 TKI with no prior platinum-based chemotherapy or immunotherapy, the median age was 57 years (range 33 to 78), while 67.9% were female, 48.2% were Asian, 64.3% had never smoked, and 67.9% had ECOG performance status of 1 at baseline. At baseline, 98.2% had metastatic disease, 42.9% had CNS metastases by BICR, and 94.6% had adenocarcinoma.

The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) per RECIST v1.1 as assessed by BICR. Intracranial response per modified RECIST v1.1 was assessed by BICR. Efficacy results are presented in the table below, which was adapted from the prescribing information.

	ROS1 Inhibitor naïve patients (N=71)	ROS1 inhibitor pretreated patients (N=56)
Confirmed ORR, %	79%	38%
Complete Response	6%	5%
Partial Response	73%	32%
Duration of Response (based on the updated data as of 12/19/22)		
Median in months	34.1	14.8
Range (months)	1.4+, 42.4+	3.6, 22.9+
% DOR ≥12 months	70%	48%

Among TKI-naïve patients, 8 had measurable CNS metastases at baseline as assessed by BICR; responses in intracranial lesions were observed in 7 of these 8 patients. Among the TKI pretreated patients with no prior platinum-based chemotherapy, 12 had measurable CNS metastases at baseline as assessed by BICR; responses in intracranial lesions were observed in 5 of these 12 patients.

Among the 56 ROS1 inhibitor-pretreated patients, 8 had resistance mutations following TKI therapy. Responses were observed in 6 of these 8 patients; responders included patients with solvent front (G2032R), gatekeeper (L2026M), and other mutations (S1986F/Y).

Place in Therapy: Augtyro® is an oral kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC). Select patients for treatment of locally advanced or metastatic NSCLC with Augtyro® based on the presence of *ROS1* rearrangement(s) in tumor specimens. An FDA-approved test to detect *ROS1* rearrangements for selecting patients for treatment with Augtyro® is not currently available. Prior to starting treatment, assess liver function tests (including bilirubin) and uric acid levels. The safety and efficacy of Augtyro® were assessed in a single-arm, open-label, multi-cohort study that included patients with *ROS1*-positive locally advanced or metastatic NSCLC. The confirmed overall response rate (ORR) for the cohort of ROS1 inhibitor naïve patients (N=71) was 79%, while the confirmed ORR in the cohort of ROS1 inhibitor pretreated patients was 38%.

It is recommended that Augtyro® should be non-recommended in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Augtyro [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2023.