Managing Dizziness

A resource for your practice, to assist with patient care

AUGTYRO™
(repotrectinib) 40 mg capsules

AUGTYRO is indicated for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC).

ROS1=proto-oncogene C-Ros1, receptor tyrosine kinase.

IMPORTANT SAFETY INFORMATION

Warnings & Precautions

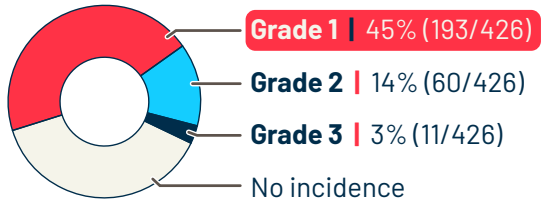
Central Nervous System Adverse Reactions

- Among the 426 patients who received AUGTYRO in Study TRIDENT-1, a broad spectrum of central nervous system (CNS) adverse reactions including dizziness, ataxia, and cognitive disorders occurred in 77% of patients with Grade 3 or 4 events occurring in 4.5%.

Please see additional Important Safety Information throughout and U.S. Full Prescribing Information for AUGTYRO.

Dizziness can occur with AUGTYRO.†[1] Here's some important management information.

In the pivotal TRIDENT-1 study,* dizziness was primarily Grade 1[2]



Dizziness generally occurred early in treatment[2,3]

Median time to onset	**7 days** (range of 1 day to 1.4 years)
Median time to resolution	**32.1 weeks**

Recommended dosing schedule for AUGTYRO[1]

Day 1-14 160 mg QD

Day 15 onward 160 mg BID

- 79% of patients in TRIDENT-1 titrated to BID dosing[2]
- Patients should continue on treatment until unacceptable toxicity or disease progression[1]

*Data from the TKI-naïve cohort of the pivotal TRIDENT-1 study, a Phase 1/2 multicenter, single-arm, open-label, multicohort clinical trial of AUGTYRO (160 mg orally once daily for 14 days, then increased to 160 mg twice daily until disease progression or unacceptable toxicity) in adult patients with locally advanced or metastatic *ROS1*+ NSCLC. The pooled safety population included 426 patients who were exposed to AUGTYRO. Adverse reactions were based on NCI CTCAE v4.03.[1]

†As reported in the AUGTYRO U.S. Prescribing Information, incidence of dizziness in the pivotal TRIDENT-1 study (N=426), regardless of grade, was 65%.[1]

CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; NSCLC=non-small cell lung cancer; ROS1=proto-oncogene C-Ros1, receptor tyrosine kinase; TKI=tyrosine kinase inhibitor.

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Tips to consider for your patients experiencing dizziness[1,4]

Drink plenty of fluids. Aim for 8 to 12 eight-ounce glasses of water or other fluids each day[4]

Avoid drinking a lot of coffee, tea, soda, and other beverages with caffeine[4]

Change positions slowly. For example, sit up carefully from a lying position. If you get dizzy when you stand up, hold a chair or table for balance and stand up more slowly than usual[4]

Walk slowly and carefully if you are dizzy. Hold handrails when using stairs[4]

Consider using a walking stick or cane to help you keep your balance[4]

Avoid driving if you are often dizzy. Do not drive or operate machinery until your symptoms have resolved[1]

IMPORTANT SAFETY INFORMATION (CONT'D)

Warnings & Precautions

Central Nervous System Adverse Reactions

- Among the 426 patients who received AUGTYRO in Study TRIDENT-1, a broad spectrum of central nervous system (CNS) adverse reactions including dizziness, ataxia, and cognitive disorders occurred in 77% of patients with Grade 3 or 4 events occurring in 4.5%.

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Counseling patients on dizziness

Remind your patients to report any dizziness to their care team

This is especially important if the dizziness gets worse, or the patient has other symptoms that need immediate medical attention, including:

- A headache that does not go away[4]
- Chest pain[4]
- Vision changes[4]
- Hearing changes[4]
- Racing heartbeat[4]
- Uncontrolled nausea and vomiting[4]
- Fever[4]
- Stroke-like symptoms[4,5]

IMPORTANT SAFETY INFORMATION (CONT'D)

Central Nervous System Adverse Reactions (cont'd)

- Dizziness, including vertigo, occurred in 65%; Grade 3 dizziness occurred in 2.8% of patients. The median time to onset was 7 days (1 day to 1.4 years). Dose interruption was required in 9% of patients, and 11% required dose reduction of AUGTYRO due to dizziness.
- Ataxia, including gait disturbance and balance disorder, occurred in 28% of patients; Grade 3 ataxia occurred in 0.5%. The median time to onset was 15 days (1 day to 1.4 years). Dose interruption was required in 5% of patients, 8% required dose reduction and one patient (0.2%) permanently discontinued AUGTYRO due to ataxia.

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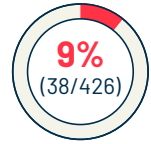
In the pivotal TRIDENT-1 study, dizziness was managed through dose reductions or interruptions depending on severity[1,3]

Dose reductions[1]

Dose interruptions[1]



Discontinuation due to dizziness[3]

0 Patients

Recommended dosage reductions with AUGTYRO[1]

Adjustable dosing allows for dose modification if needed for adverse reactions

Recommended Dosage Reductions for Adverse Reactions[1]		
Dose	Dose Reduction	
	First	Second
160 mg once daily	120 mg once daily	80 mg once daily
160 mg twice daily	120 mg twice daily	80 mg twice daily

A prescription for **40-mg capsules** is required for dose reductions[1]

Recommended Dosage Adjustments for Dizziness[1]	
Intolerable Grade 2	Withhold AUGTYRO until ≤Grade 1 or baseline, then resume at same or reduced dose, as clinically appropriate
Grade 3	Withhold AUGTYRO until ≤Grade 1 or baseline, then resume at reduced dose
Grade 4	Permanently discontinue AUGTYRO

IMPORTANT SAFETY INFORMATION (CONT'D)

Central Nervous System Adverse Reactions (cont'd)

- Cognitive impairment, including memory impairment and disturbance in attention, occurred in 25% of patients. Cognitive impairment included memory impairment (15%), disturbance in attention (12%), and confusional state (2%); Grade 3 cognitive impairment occurred in 0.9% of patients. The median time to onset of cognitive disorders was 37 days (1 day to 1.4 years). Dose interruption was required in 2% of patients, 2.1% required dose reduction and 0.5% permanently discontinued AUGTYRO due to cognitive adverse reactions.

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IMPORTANT SAFETY INFORMATION (CONT'D)

Central Nervous System Adverse Reactions (cont'd)

- Mood disorders occurred in 6% of patients. Mood disorders occurring in >1% of patients included anxiety (2.6%); Grade 4 mood disorders (mania) occurred in 0.2% of patients. Dose interruption was required in 0.2% of patients and 0.2% required a dose reduction due to mood disorders.
- Sleep disorders including insomnia and hypersomnia occurred in 18% of patients. Sleep disorders observed in >1% of patients were somnolence (9%), insomnia (6%) and hypersomnia (1.6%). Dose interruption was required in 0.7% of patients, and 0.2% required a dose reduction due to sleep disorders.
- The incidences of CNS adverse reactions reported were similar in patients with and without CNS metastases.
- Advise patients not to drive or use machines if they are experiencing CNS adverse reactions. Withhold and then resume at same or reduced dose upon improvement, or permanently discontinue AUGTYRO based on severity.

Interstitial Lung Disease (ILD)/Pneumonitis

- Among the 426 patients treated with AUGTYRO, ILD/pneumonitis (pneumonitis [2.8%] and ILD [0.2%]) occurred in 3.1%; Grade 3 ILD/pneumonitis occurred in 1.2%. The median time to onset was 45 days (19 days to 0.9 years). Dose interruption was required in 1.4% of patients, 0.5% required dose reduction, and 1.1% permanently discontinued AUGTYRO due to 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.

Hepatotoxicity

- Among the 426 patients treated with AUGTYRO, increased alanine transaminase (ALT) occurred in 38%, increased aspartate aminotransferase (AST) occurred in 41%, including Grade 3 or 4 increased ALT in 3.3% and increased AST in 2.9%. The median time to onset of increased ALT or AST was 15 days (range: 1 day to 1.9 years). Increased ALT or AST leading to dose interruptions or reductions occurred in 2.8% and 1.2% of patients, respectively. Hyperbilirubinemia leading to dose interruptions occurred in 0.5%.
- Monitor liver function tests, including ALT, AST and bilirubin, every 2 weeks during the first month of treatment, then monthly thereafter and then as clinically indicated. Withhold and then resume at same or reduced dose upon improvement or permanently discontinue AUGTYRO based on the severity.

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Myalgia with Creatine Phosphokinase (CPK) Elevation

- AUGTYRO can cause myalgia with or without creatine phosphokinase (CPK) elevation. Among the 426 patients treated with AUGTYRO, myalgia occurred in 13% of patients, with Grade 3 in 0.7%. Median time to onset of myalgia was 19 days (range: 1 day to 2 years). Concurrent increased CPK within a 7-day window was observed in 3.7% of patients. AUGTYRO was interrupted in one patient with myalgia and concurrent 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 same or reduced dose upon improvement.

Hyperuricemia

- Among the 426 patients treated with AUGTYRO, 21 patients (5%) experienced hyperuricemia reported as an adverse reaction, 0.7% experienced Grade 3 or 4 hyperuricemia. One patient without pre-existing gout required urate-lowering medication.
- Monitor serum uric acid levels prior to initiating AUGTYRO and periodically during treatment. Initiate treatment with urate-lowering medications as clinically indicated. Withhold and then resume at same or reduced dose upon improvement, or permanently discontinue AUGTYRO based on severity.

Skeletal Fractures

- Among 426 adult patients who received AUGTYRO, fractures occurred in 2.3%. Fractures involved the ribs (0.5%), feet (0.5%), spine (0.2%), acetabulum (0.2%), sternum (0.2%), and ankles (0.2%). Some fractures occurred at sites of disease and prior radiation therapy. The median time to fracture was 71 days (range: 31 days to 1.4 years). AUGTYRO was interrupted in 0.3% of patients.
- Of 26 evaluable patients in an ongoing open-label study in pediatric patients, fractures occurred in one 12- year-old patient (ankle/foot) and one 10-year-old patient (stress fracture). AUGTYRO was interrupted in both patients. AUGTYRO is not approved for use in pediatric patients less than 12 years of age.
- Promptly evaluate patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures. There are no data on the effects of AUGTYRO on healing of known fractures and risk of future fractures.

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IMPORTANT SAFETY INFORMATION (CONT'D)

Embryo-Fetal Toxicity

- Based on literature reports in humans with congenital mutations leading to changes in tropomyosin receptor tyrosine kinase (TRK) signaling, findings from animal studies, and its mechanism of action, AUGTYRO can cause fetal harm when administered to a pregnant woman.
- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with AUGTYRO and for 2 months following the last dose, since AUGTYRO can render some hormonal contraceptives ineffective.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment with AUGTYRO and for 4 months after the last dose.

Adverse Reactions

- The safety of AUGTYRO was evaluated in 426 patients in TRIDENT-1. The most common adverse reactions (≥20%) were dizziness, dysgeusia, peripheral neuropathy, constipation, dyspnea, fatigue, ataxia, cognitive impairment, muscular weakness, and nausea.

Drug Interactions
Effects of Other Drugs on AUGTYRO

Strong and Moderate CYP3A Inhibitors

- 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 initiating AUGTYRO.

P-gp Inhibitors

- 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.

Strong and Moderate CYP3A Inducers

- 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.

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Effects of AUGTYRO on other Drugs

Certain CYP3A4 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. Concomitant use of repotrectinib decreases the concentration of CYP3A4 substrates, which can reduce the efficacy of these substrates.

Contraceptives

- 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 of childbearing potential to use an effective nonhormonal contraceptive.

Please see U.S. Full Prescribing Information for AUGTYRO here.

References: 1. AUGTYRO [package insert]. Princeton, NJ. Bristol-Myers Squibb Company: 2024.
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)(suppl):118-131. **3.** 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.
4. Erickson AE, Klein E. What causes dizziness and how to treat it. Healthline. August 10, 2022. Accessed December 12, 2024. https://www.healthline.com/health/dizziness
5. Holland K. Everything you need to know about stroke. Healthline. November 9, 2021. Updated June 18, 2024. Accessed December 12, 2024. https://www.healthline.com/health/stroke

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Helping your patients manage adverse reactions can help them stay on AUGTYRO, as appropriate

Ask your patients to contact you and their care team if they think they are experiencing an adverse reaction

IMPORTANT SAFETY INFORMATION

SUMMARY OF WARNINGS AND PRECAUTIONS

- AUGTYRO (repotrectinib) is associated with the following warnings and precautions: central nervous system (CNS) adverse reactions, interstitial lung disease (ILD)/pneumonitis, hepatotoxicity, myalgia with creatine phosphokinase (CPK) elevation, hyperuricemia, skeletal fractures, and embryo-fetal toxicity.

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Bristol Myers Squibb®

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