IMPORTANT SAFETY INFORMATION

Warnings & Precautions

Central Nervous System Adverse Reactions

Among the 351 patients who received AUGTYRO in the TRIDENT-1 study, a broad spectrum of central nervous system (CNS) adverse reactions including dizziness, ataxia, and cognitive disorders occurred in 75% with Grade 3 or 4 events occurring in 4%. Dizziness, including vertigo, occurred in 64% and Grade 3 dizziness occurred in 2.8% of patients. The median time to onset was 6 days (1 day to 1.4 years). Dose interruption was required in 9% of patients, and 12% required dose reduction of AUGTYRO due to dizziness.

Please see Important Safety Information throughout and on pages 4-6. Please see U.S. Full Prescribing Information for AUGTYRO.
In the TKI-naive population in the pivotal TRIDENT-1 study

**AUGTYRO demonstrated durable response**

**PRIMARY ENDPOINT**

79% ORR

(n=56/71; 95% CI: 68, 88; 6% CR, 73% PR)†

Median follow-up for ORR data: 18.1 months.5

**SECONDARY ENDPOINT**

34-month mDOR

(95% CI: 25.6, NE; range: 1.4+, 42.4+ months)

Median follow-up for DOR data: 24.0 months.6

**Intracranial response with AUGTYRO**

**SECONDARY ENDPOINT**

icORR was seen in 7/8 patients with measurable CNS metastasis at baseline§

Median follow-up for icORR data: 18.1 months.6

* Durable response is based on objective response rate and median duration of response for AUGTYRO.1
† Data from the TKI-naive cohort of the pivotal TRIDENT-1 study.1
‡ CR, n=4/71; PR, n=52/71.
§ Intracranial response according to modified RECIST v1.1 was assessed by BICR. Among 71 patients in the TKI-naive cohort, 8 had measurable CNS metastases at baseline (as assessed by BICR). icORR is a secondary endpoint of the pivotal trial of AUGTYRO.15

BICR=blinded independent central review; CNS=central nervous system; CR=complete response; DOR=duration of response; icORR=intracranial objective response rate; mDOR=median duration of response; NE=not evaluable, endpoint not yet reached; NSCLC=non-small cell lung cancer; ORR=objective response rate; PR=partial response; RECIST=Response Evaluation Criteria In Solid Tumors; ROS1=proto-oncogene C-Ros1, receptor tyrosine kinase; TKI=tyrosine kinase inhibitor.

**IMPORTANT SAFETY INFORMATION**

Central Nervous System Adverse Reactions (cont’d)

- Ataxia, including gait disturbance and balance disorder, occurred in 29% of the 351 patients; Grade 3 ataxia occurred in 0.3%. The median time to onset was 15 days (1 day to 1.4 years). Dose interruption was required in 6% of patients, 8% required dose reduction and one patient (0.3%) permanently discontinued AUGTYRO due to ataxia.

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Central Nervous System Adverse Reactions (cont'd)

- Cognitive disorder, including memory impairment and disturbance in attention, occurred in 23% of the 351 patients. Cognitive disorders included memory impairment (13%), disturbance in attention (11%), and confusional state (2%); Grade 3 cognitive disorders 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, 1.7% required dose reduction and 0.6% permanently discontinued AUGTYRO due to cognitive adverse reactions.

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**IMPORTANT SAFETY INFORMATION**

**Central Nervous System Adverse Reactions (cont’d)**
- Mood disorders occurred in 6% of the 351 patients. Mood disorders occurring in >1% of patients included anxiety (2.8%), irritability (1.1%), and depression (1.4%); Grade 4 mood disorders (mania) occurred in 0.3% of patients. Dose interruption was required in 0.3% of patients and 0.3% required a dose reduction due to mood disorders.
- Sleep disorders including insomnia and hypersomnia occurred in 15% of the 351 patients. Sleep disorders observed in >1% of patients were somnolence (8%), insomnia (6%) and hypersomnia (1.1%). Dose interruption was required in 0.9% of patients, and 0.3% 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 351 patients treated with AUGTYRO, ILD/pneumonitis (pneumonitis [2.6%] and interstitial lung disease [0.3%]) occurred in 2.9%; Grade 3 ILD/pneumonitis occurred in 1.1%. The median time to onset was 45 days (19 days to 0.9 years). Dose interruption was required in 1.4% of patients, 0.6% 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 351 patients treated with AUGTYRO, increased alanine transaminase (ALT) occurred in 35%, increased aspartate aminotransferase (AST) occurred in 40%, including Grade 3 or 4 increased ALT in 2% and increased AST in 2.6%. 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 1.4% of patients, respectively. Hyperbilirubinemia leading to dose interruptions occurred in 0.6%.
- 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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IMPORTANT SAFETY INFORMATION

Myalgia with Creatine Phosphokinase (CPK) Elevation
- Among the 351 patients treated with AUGTYRO, myalgia occurred in 13% of patients, with Grade 3 in 0.6%. 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 351 patients treated with AUGTYRO, 18 patients (5%) experienced hyperuricemia reported as an adverse reaction, 0.9% 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 351 adult patients who received AUGTYRO, fractures occurred in 2.3%. Fractures involved the ribs (0.6%), feet (0.6%), spine (0.3%), acetabulum (0.3%), sternum (0.3%), and ankles (0.3%). 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.
- 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.

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.

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IMPORTANT SAFETY INFORMATION

Adverse Reactions
• Among 351 patients who received AUGTYRO for ROS1-positive NSCLC and other solid tumors in the TRIDENT-1 trial, the most common (>20%) adverse reactions were dizziness (64%), dysgeusia (50%), peripheral neuropathy (47%), constipation (37%), dyspnea (30%), ataxia (29%), fatigue (29%), cognitive disorders (23%), and nausea (20%).
• In a subset of 264 patients who received AUGTYRO for ROS1-positive NSCLC, the most common (≥20%) adverse reactions were dizziness (63%), dysgeusia (48%), peripheral neuropathy (47%), constipation (36%), dyspnea (30%), ataxia (28%), fatigue (24%), cognitive disorders (23%), and muscular weakness (21%).

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.

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.

Ropotrectinib 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 to use an effective nonhormonal contraceptive.

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Bristol Myers Squibb is committed to transparency. For information on the list price of AUGTYRO as well as information regarding average out-of-pocket costs and assistance programs, please visit our pricing information page.

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