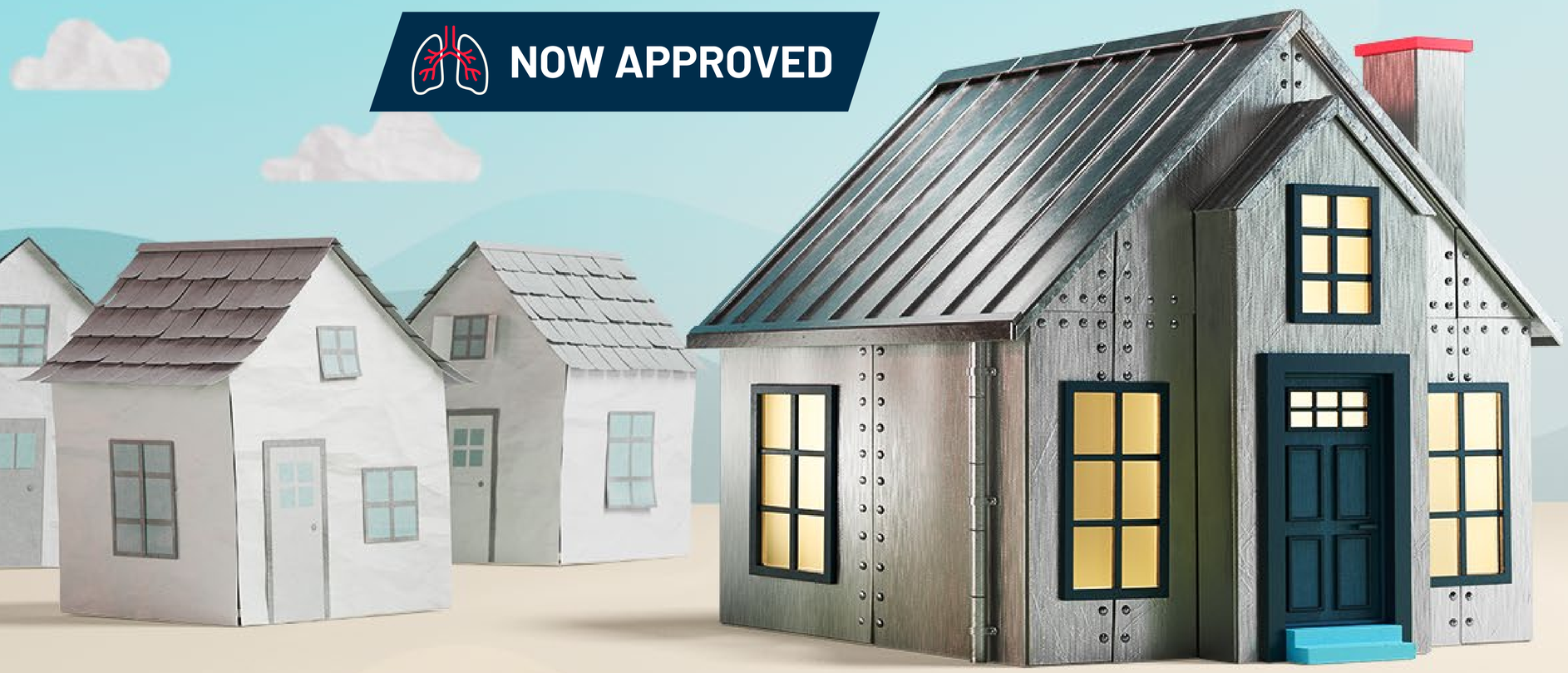
AUGTYRO™ (repotrectinib) 40 mg capsules

NOW APPROVED

Define durability*

The **next-generation TKI** for ***ROS1+* NSCLC**[1-4†]



*Durable response is based on objective response rate and median duration of response for AUGTYRO.[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 major efficacy outcome measures were ORR and DOR (assessed by BICR per RECIST v1.1). Efficacy population included patients who received at least 1 dose of AUGTYRO.[1]

BICR=blinded independent central review; DOR=duration of response; NSCLC=non-small cell lung cancer; ORR=objective response rate; RECIST=Response Evaluation Criteria In Solid Tumors; ROS1=proto-oncogene C-Ros1, receptor tyrosine kinase; TKI= tyrosine kinase inhibitor.

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

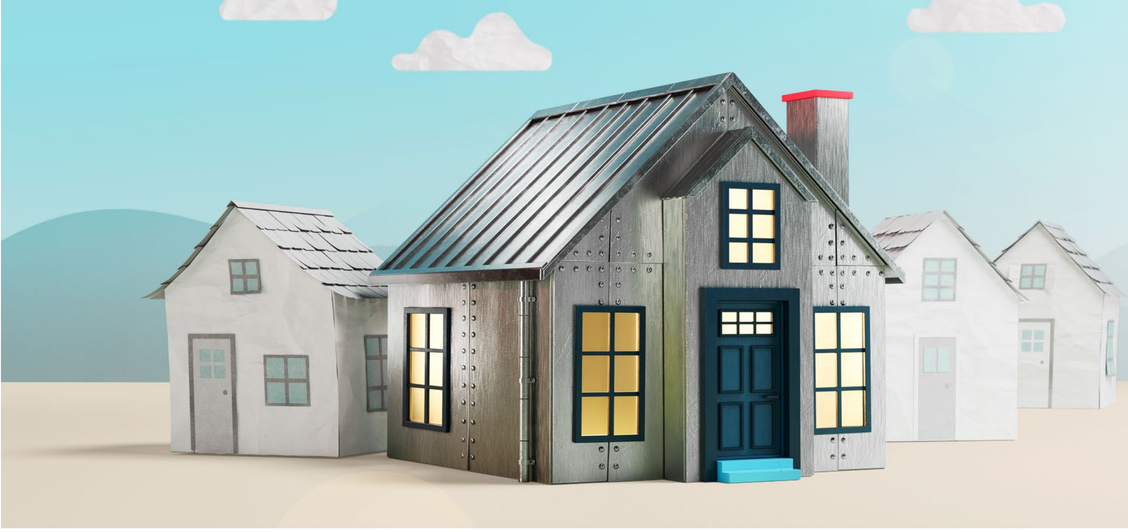
IMPORTANT SAFETY INFORMATION

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.



Define durability* with AUGTYRO™

The **next-generation TKI** for ***ROS1+* NSCLC**[1-4†]

In the **TKI-naïve population** in the pivotal **TRIDENT-1** study†

AUGTYRO demonstrated durable response[1,5,6*]

PRIMARY ENDPOINT

79% ORR[1,5*†]

(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[1,6*†]

(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[1§]

Median follow-up for icORR data: 18.1 months.[5]

*Durable response is based on objective response rate and median duration of response for AUGTYRO.[1]
†Data from the TKI-naïve cohort of the pivotal TRIDENT-1 study.[1]
‡CR, n=4/71; PR, n=52/71.[5]
§Intracranial response according to modified RECIST v1.1 was assessed by BICR. Among 71 patients in the TKI-naïve cohort, 8 had measurable CNS metastases at baseline (as assessed by BICR). icORR is a secondary endpoint of the pivotal trial of AUGTYRO.[1,5]

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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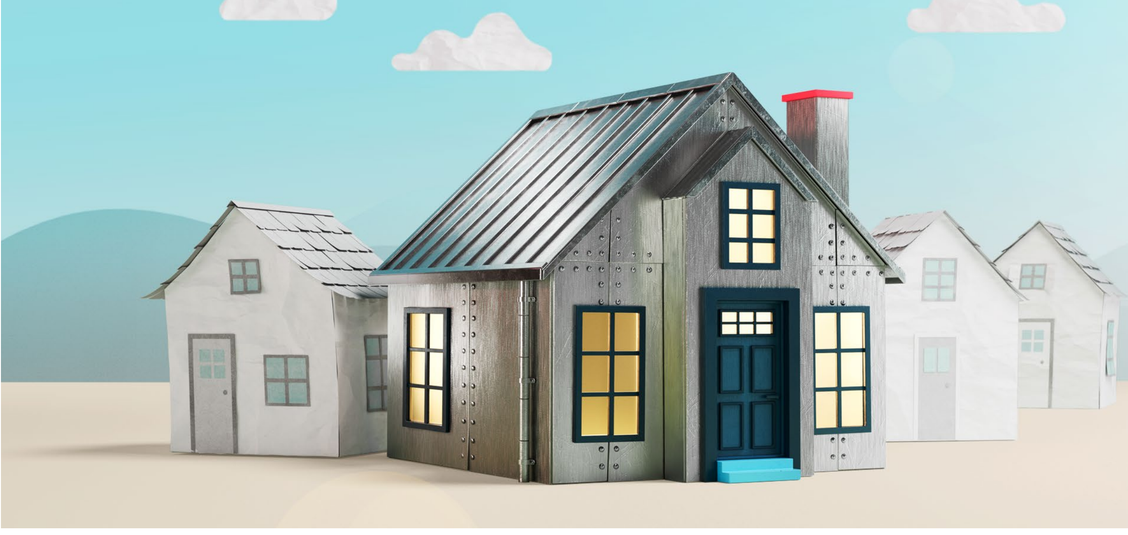

Explore more data from TRIDENT-1

Noncomparative mPFS in the TKI-naïve population

SECONDARY ENDPOINT

35.7-month mPFS[6] (95% CI: 27.4, NE)

Median follow-up for PFS data: 24.0 months.[6]

Single-arm studies cannot adequately characterize time-to-event endpoints such as PFS. As such, the clinical significance of these data is not known. These data are not included in the AUGTYRO U.S. Prescribing Information, and this analysis should be interpreted with caution.

ROS1+ NSCLC safety (n=264) in the pivotal TRIDENT-1 study included*:

- 8% of patients permanently discontinued AUGTYRO[1]
- Serious adverse reactions occurred in 33% and included pneumonia, dyspnea, pleural effusion, and hypoxia in ≥2% of patients[1]

Interested in bringing this next-generation TKI to your *ROS1*+ NSCLC patients?
Scan the QR code or visit **AUGTYROhcp.com** to learn more about AUGTYRO.

*The *ROS1*+ NSCLC safety population included 264 patients from the Phase 2 study cohorts, who received the recommended dose of AUGTYRO.[1]

mPFS=metastatic progression-free survival; NE=not evaluable, endpoint not yet reached; NSCLC=non-small cell lung cancer; PFS=progression-free survival; ROS1=proto-oncogene C-Ros1, receptor tyrosine kinase; TKI= tyrosine kinase inhibitor.

IMPORTANT SAFETY INFORMATION

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.
- 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 to use an effective nonhormonal contraceptive.

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References: 1. AUGTYRO [package insert]. Princeton, NJ. Bristol-Myers Squibb Company. **2.** Yun MR, Kim DH, Kim SY, et al. Repotrectinib exhibits potent antitumor activity in treatment-naïve and solvent-front-mutant ROS1-rearranged non-small cell lung cancer. *Clin Cancer Res.* 2020;26(13):3287-3295. **3.** Murray BW, Rogers E, Zhai D, et al. Molecular characteristics of repotrectinib that enable potent inhibition of TRK fusion proteins and resistant mutations. *Mol Cancer Ther.* 2021;20(12):2446-2456. **4.** Drilon A, Ou SI, Cho BC, et al. Repotrectinib (TPX-0005) is a next-generation ROS1/TRK/ALK inhibitor that potently inhibits ROS1/TRK/ALK solvent-front mutations. *Cancer Discov.* 2018;8(10):1227-1236. **5.** Cho BC, Lin JJ, Camidge DR, et al. Pivotal topline data from the phase 1/2 TRIDENT-1 trial of repotrectinib in patients with *ROS1*+ advanced non-small cell lung cancer (NSCLC). *Eur J Cancer.* 2022;174(suppl1):S1–S2. **6.** Cho BC, Camidge DR, Lin JJ, et al. Repotrectinib in patients with *ROS1* fusion-positive non-small cell lung cancer: update from the pivotal phase 1/2 TRIDENT-1 trial. Presented at: 2023 World Conference on Lung Cancer; September 9-12, 2023; Singapore.

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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