HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AUGTYRO safely and effectively. See full prescribing information for AUGTYRO.

AUGTYRO™ (repotrectinib) capsules, for oral use
Initial U.S. Approval: 2023

----------INDICATIONS AND USAGE----------

AUGTYRO is a kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC). (1)

----------DOSAGE AND ADMINISTRATION----------

- Select patients for the treatment of locally advanced or metastatic NSCLC based on the presence of *ROS1* rearrangement(s) in tumor specimens. (2.1)
- Recommended Dosage: 160 mg orally once daily for 14 days, then increase to 160 mg twice daily, with or without food. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 40 mg (3)

----------CONTRAINDICATIONS----------

None

----------WARNINGS AND PRECAUTIONS----------

- Central Nervous System (CNS) Effects: Can cause CNS adverse reactions including dizziness, ataxia, and cognitive impairment. Withhold and then resume at same or reduced dose upon improvement, or permanently discontinue AUGTYRO based on severity. (5.1)
- Interstitial Lung Disease (ILD)/Pneumonitis: Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed. (5.2)
- Hepatotoxicity: Monitor liver function tests every 2 weeks during the first month of treatment, and as clinically indicated thereafter. Based on severity, withhold and then resume at same or reduced dose, or permanently discontinue. (5.3)
- Myalgia with Creatine Phosphokinase (CPK) Elevation: Monitor serum CPK levels during treatment in patients reporting unexplained muscle pain, tenderness, or weakness. Based on severity, withhold and resume at same or reduced dose upon improvement. (5.4)
- Hyperuricemia: Monitor serum uric acid levels prior to initiating and periodically during treatment. Initiate treatment with urate-lowering medications as clinically indicated. Withhold and resume at same or reduced dose, or permanently discontinue based on severity. (5.5)
- Skeletal Fractures: Promptly evaluate patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures. (5.6)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use an effective non-hormonal method of contraception. (5.7)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥20%) were dizziness, dysgeusia, peripheral neuropathy, constipation, dyspnea, ataxia, fatigue, cognitive disorders, and muscular weakness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong and Moderate CYP3A Inhibitors: Avoid concomitant use. (7.1)
- P-gp inhibitors: Avoid concomitant use. (7.1)
- Strong and Moderate CYP3A Inducers: Avoid concomitant use. (7.1)
- Certain CYP3A Substrates: Avoid concomitant use with CYP3A substrates, where minimal concentration changes can cause reduced efficacy. (7.2)
- Hormonal contraceptives: Avoid concomitant use. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved-patient labeling.

Revised: 11/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AUGTYRO is indicated for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC) *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of locally advanced or metastatic NSCLC with AUGTYRO based on the presence of *ROS1* rearrangement(s) in tumor specimens *[see Clinical Studies (14.1)]*. An FDA-approved test to detect *ROS1* rearrangements for selecting patients for treatment with AUGTYRO is not currently available.

2.2 Important Information Prior to Initiating AUGTYRO

Prior to initiating AUGTYRO, discontinue strong and moderate CYP3A inhibitors for 3 to 5 elimination half-lives of the CYP3A inhibitor *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

2.3 Recommended Evaluation and Testing Before Initiating AUGTYRO

Prior to initiation of AUGTYRO, evaluate:

- liver function tests including bilirubin *[see Warnings and Precautions (5.3)]*
- uric acid level *[see Warnings and Precautions (5.5)]*

2.4 Recommended Dosage

The recommended dosage of AUGTYRO is 160 mg taken orally once daily with or without food *[see Clinical Pharmacology (12.3)]* for 14 days, then increase to 160 mg twice daily and continue until disease progression or unacceptable toxicity.

2.5 Dosage Modifications for Adverse Reactions

The recommended dosage reductions of AUGTYRO for the management of adverse reactions are provided in Table 1.

Table 1: Recommended Dose Reductions for AUGTYRO Adverse Reactions

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

Recommended dosage modifications of AUGTYRO for the management of adverse reactions are provided in Table 2.

Table 2: Recommended Dosage Modifications for AUGTYRO Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
Central Nervous System Effects *[see Warnings and Precautions (5.1)]*	Intolerable Grade 2	• Withhold AUGTYRO until ≤Grade 1 or baseline. • Resume at same or reduced dose, as clinically appropriate.
	Grade 3	• Withhold AUGTYRO until ≤Grade 1 or baseline. • Resume at reduced dose.
	Grade 4	• Permanently discontinue AUGTYRO.
Interstitial Lung Disease (ILD)/Pneumonitis *[see Warnings and Precautions (5.2)]*	Any Grade	• Withhold AUGTYRO if ILD/pneumonitis is suspected. • Permanently discontinue if ILD/pneumonitis is confirmed.
Hepatotoxicity *[see Warnings and Precautions (5.3)]*	Grade 3	• Withhold AUGTYRO until ≤ Grade 1 or baseline. • Resume at same dose if resolution occurs within 4 weeks. • Resume at a reduced dose for recurrent Grade 3 events that resolve within 4 weeks.
	Grade 4	• Withhold AUGTYRO until ≤ Grade 1 or baseline. • Resume at reduced dose. • Permanently discontinue if adverse reaction does not resolve within 4 weeks. • Permanently discontinue for recurrent Grade 4 events.
	ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 1.5 times ULN (in the absence of cholestasis or hemolysis)	• Permanently discontinue AUGTYRO.
Creatine Phosphokinase (CPK) Elevation *[see Warnings and Precautions (5.4)]*	CPK elevation greater than 5 times ULN	• Withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at same dose.

	CPK elevation greater than 10 times ULN or second occurrence of CPK elevation of greater than 5 times ULN	• Withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at reduced dose.
Hyperuricemia *[see Warnings and Precautions (5.5)]*	Grade 3 or Grade 4	• Withhold AUGTYRO until improvement of signs or symptoms. • Resume AUGTYRO at same or reduced dose.
Other Clinically Relevant Adverse Reactions *[see Adverse Reactions (6.1)]*	Intolerable Grade 2 or Grade 3 or Grade 4	• Withhold AUGTYRO until ≤Grade 1 or baseline. • Resume at the same or reduced dose if resolution occurs within 4 weeks. • Permanently discontinue if adverse reaction does not resolve within 4 weeks. • Permanently discontinue for recurrent Grade 4 events.

*Graded per Common Terminology Criteria for Adverse Events v4.03

2.6 Administration

Take AUGTYRO at approximately the same time each day with or without food *[see Pharmacokinetics (12.3)]*.

Swallow AUGTYRO capsules whole. Do not open, chew, crush, or dissolve the capsule prior to swallowing. Do not take any AUGTYRO capsules that are broken, cracked, or damaged.

If a dose of AUGTYRO is missed or if vomiting occurs at any time after taking a dose, skip the dose and resume AUGTYRO at its regularly scheduled time.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 40 mg, white, opaque, immediate release, Size 0, hard shell capsule, filled with white to off-white powder which may appear as a plug, imprinted with “REP 40” in blue text on the cap.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Central Nervous System Adverse Reactions

AUGTYRO can cause central nervous system adverse reactions.

Among the 351 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 75% with Grade 3 or 4 events occurring in 4% of patients.

Dizziness, including vertigo, occurred in 64% of the 351 patients; 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.

Ataxia, including gait disturbance and balance disorder, occurred in 29% of the 351 patients; Grade 3 ataxia occurred in 0.3% of patients. 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.

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% patients permanently discontinued AUGTYRO due to cognitive adverse reactions.

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% of patients 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% of patients required a dose reduction due to sleep disorders.

The incidences of CNS adverse reactions observed were similar in patients with and without CNS metastases.

Advise patients and caregivers of the risk of CNS adverse reactions with AUGTYRO. 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 *[see Dosage and Administration (2.5)]*.

5.2 Interstitial Lung Disease/Pneumonitis

AUGTYRO can cause 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% of patients; Grade 3 ILD/pneumonitis occurred in 1.1% of patients. 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% of patients required dose reduction, and 1.1% of patients 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 *[see Dosage and Administration (2.5)]*.

5.3 Hepatotoxicity

AUGTYRO can cause 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 as clinically indicated. Withhold and then resume at the same or reduced dose upon improvement, or permanently discontinue AUGTYRO based on the severity *[see Dosage and Administration (2.5)]*.

5.4 Myalgia with Creatine Phosphokinase Elevation

AUGTYRO can cause myalgia with or without 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 the same or reduced dose upon improvement *[see Dosage and Administration (2.5)]*.

5.5 Hyperuricemia

AUGTYRO can cause hyperuricemia.

Among the 351 patients treated with AUGTYRO, 18 patients (5%) experienced hyperuricemia reported as an adverse reaction and 0.9% of patients 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 the same or reduced dose upon improvement, or permanently discontinue AUGTYRO based on severity *[see Dosage and Administration (2.5)]*.

5.6 Skeletal Fractures

AUGTYRO can cause 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.

5.7 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.

Oral administration of repotrectinib to pregnant rats during the period of organogenesis resulted in fetal malformations at doses approximately 0.3 times the recommended 160 mg twice daily dose based on body surface area (BSA).

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 *[see Drug Interactions (7.2)]*. 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 *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Central Nervous System Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Interstitial Lung Disease (ILD)/Pneumonitis *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Myalgia with Creatine Phosphokinase Elevation *[see Warnings and Precautions (5.4)]*
- Hyperuricemia *[see Warnings and Precautions (5.5)]*
- Skeletal Fractures *[see Warnings and Precautions (5.6)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates reported in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in WARNINGS AND PRECAUTIONS reflects exposure to AUGTYRO as a single agent dosed at 160 mg orally once daily for 14 days, then increased to 160 mg twice daily until disease progression or unacceptable toxicity in 351 patients with *ROS1*-positive NSCLC and other solid tumors in the TRIDENT-1 trial. Among 351 patients who received AUGTYRO, 52% were exposed for 6 months or longer and 26% were exposed for greater than 1 year. In this pooled safety population, 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%). The most common (≥2%) Grade 3 or 4 laboratory abnormalities were increased gamma glutamyl transferase (13%), decreased lymphocytes (10%), increased urate (10%), decreased neutrophils (8%), decreased hemoglobin (7%), increased creatine phosphokinase (5.8%), decreased phosphate (4.9%), decreased leukocytes (3.8%), increased ALT (3.5%), decreased sodium (3.5%), increased AST (2.9%), increased magnesium (2.9%), increased alkaline phosphatase (2.6%), and increased glucose (2%).

TRIDENT-1

The safety of AUGTYRO was evaluated in 264 patients with *ROS1*-positive NSCLC in TRIDENT-1 *[see Clinical Studies (14.1)]*. Eligible patients had an ECOG status of ≤1. Patients with a history of ILD, drug-related pneumonitis, significant, uncontrolled, active cardiovascular disease, or prolonged QTc interval were excluded from enrollment in this trial. Patients received AUGTYRO at a dose of 160 mg orally once daily for the first 14 days, then increased to 160 mg orally twice daily until disease progression or unacceptable toxicity. Among patients who received AUGTYRO, 52% were exposed for at least 6 months, and 27% were exposed for greater than 1 year.

The median age of patients who received AUGTYRO was 56 years (range: 27 to 93); 62% female; 43% White, 49% Asian, 2.7% Black, 0.8% Native Hawaiian or Other Pacific Islander, 0.4% American Indian or Alaska Native, 3.4% race not reported, and 1.1% unknown.

Serious adverse reactions occurred in 33% of patients who received AUGTYRO. Serious adverse reactions in ≥2% of patients included pneumonia (5.7%), dyspnea (3.8%), pleural effusion (3.4%), and hypoxia (3%). Fatal adverse reactions occurred in 4.2% of patients who received AUGTYRO, including death, pneumonia, pneumonia aspiration, cardiac arrest, sudden cardiac death, cardiac failure, sudden death, hypoxia, dyspnea, respiratory failure, tremor, and disseminated intravascular coagulation.

Permanent discontinuation of AUGTYRO was required in 8% of patients due to adverse reactions. The adverse reactions resulting in permanent discontinuation of AUGTYRO in ≥1% of patients were dyspnea, pneumonitis, and muscular weakness.

Dosage interruptions of AUGTYRO due to an adverse reaction occurred in 48% of patients. Adverse reactions that required dosage interruption in ≥5% of patients included CNS toxicity, dyspnea, and muscular weakness.

Dose reductions of AUGTYRO due to an adverse reaction occurred in 35% of patients. Adverse reactions that required dosage reductions in ≥5% of patients included dizziness.

The most common adverse reactions (≥20%) were dizziness, dysgeusia, peripheral neuropathy, constipation, dyspnea, ataxia, fatigue, cognitive disorders, and muscular weakness. The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased hemoglobin, decreased lymphocytes, decreased leukocytes, increased alanine aminotransferase, decreased neutrophils, increased gamma glutamyl transferase, increased alkaline phosphatase, increased urate, increased magnesium, and decreased phosphate. Table 3 summarizes the adverse reactions in the TRIDENT-1 trial.

Table 3: Adverse Reactions (≥10%) in Patients with ROS1-positive NSCLC Who Received AUGTYRO in TRIDENT-1

Adverse Reaction[1]	AUGTYRO N=264	
	All Grades (%)	Grade 3 or 4 (%)
Nervous System Disorders		
Dizziness[a]	63	1.9
Dysgeusia[b]	48	0
Peripheral neuropathy[c]	47	1.9
Ataxia[d]	28	0.4
Cognitive disorders[e]	23	0.8
Headache[f]	19	0
Gastrointestinal Disorders		
Constipation	36	0
Nausea	19	0.4
Diarrhea	13	0.4
Vomiting	10	0.8
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea[g]	30	7
Cough[h]	14	0
General Disorders		
Fatigue[i]	24	1.1
Edema[j]	12	0.8
Musculoskeletal and Connective Tissue Disorders		
Muscular weakness	21	1.5
Myalgia[k]	12	0.4
Metabolism and Nutritional		
Increased weight	14	1.9
Eye Disorders		
Vision disorders[l]	11	0

[1] Based on NCI CTCAE v4.03

[a] Includes terms dizziness, vertigo, dizziness postural, dizziness exertional, vertigo positional

[b] Includes terms dysgeusia, ageusia, anosmia, hypogeusia

[c] Includes terms neuralgia, neuropathy peripheral, peripheral sensory neuropathy, dysesthesia, peripheral motor neuropathy, polyneuropathy, paresthesia, hypoesthesia, hyperesthesia

[d] Includes terms ataxia, gait disturbance, balance disorder, cerebellar ataxia

[e] Includes terms memory impairment, disturbance in attention, cognitive disorder, confusional state, amnesia, attention deficit hyperactivity disorder, delirium, altered state of consciousness, aphasia, delusion, depressed level of consciousness, hallucination, mental status changes, neurological decompensation

[f] Includes terms headache, migraine, tension headache

[g] Includes terms dyspnea and dyspnea exertional

[h] Includes terms productive cough, cough, and upper-airway cough syndrome

[i] Includes terms fatigue and asthenia

[j] Includes terms generalized edema, periorbital edema, localized edema, face edema, edema peripheral, edema, eye edema, scrotal edema

[k] Includes terms myalgia, myositis, musculoskeletal discomfort, musculoskeletal pain

[1] Includes terms vision blurred, dry eye, visual impairment, visual field defect, cataract, conjunctivitis, eye pain, photophobia, photosensitivity reaction, visual acuity reduced, vitreous floaters, blepharospasm, color blindness, diplopia, eye hematoma, eye swelling, eyelid disorder, eyelid injury, eyelids pruritus, glaucoma, night blindness, ophthalmic herpes zoster

Clinically relevant adverse reactions in <10% of patients receiving AUGTYRO were pyrexia (8%) and fall (2.7%).

Table 4 summarizes the laboratory abnormalities.

Table 4: Select Laboratory Abnormalities (≥20%) That Worsened from Baseline in Patients with ROS1-positive NSCLC Who Received AUGTYRO in TRIDENT-1

Laboratory Abnormality[1]	**AUGTYRO[2] N=264**	
	All Grades (%)	**Grade 3 or 4 (%)**
Hematology		
Decreased Hemoglobin	73	5
Decreased Lymphocytes	43	10
Decreased Leukocytes	36	4.7
Decreased Neutrophils	34	8
Increased aPTT	25	0.4
Increased INR	20	0
Chemistry		
Increased Creatine Phosphokinase	57	6
Increased GGT	48	12
Increased AST	40	1.9
Increased ALT	34	3.1
Increased Sodium	29	0.4
Increased Alkaline Phosphatase	26	2.3
Increased Glucose	23	1.5
Increased Urate	21	11
Decreased Glucose	21	0.4

Abbreviations: AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; GGT: Gamma Glutamyl Transferase; aPTT: Activated Partial Thromboplastin Time; INR: Prothrombin International Normalized Ratio

[1] Based on NCI CTCAE v4.03

[2] The denominator used to calculate the rate varied from 163 to 261 based on the number of patients with a baseline value and at least one post-treatment value.

7 DRUG INTERACTIONS

7.1 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 *[see Clinical Pharmacology (12.3)]*.

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 *[see Clinical Pharmacology (12.3)]*.

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 *[see Clinical Pharmacology (12.3)]*.

7.2 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 *[see Clinical Pharmacology (12.3)]*, 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 *[see Use in Specific Populations (8.1, 8.3)]*. Advise females to use an effective nonhormonal contraceptive.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on literature reports in humans with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action *[see Clinical Pharmacology (12.1)]*, AUGTYRO can cause fetal harm when administered to a pregnant woman. There are no available data on AUGTYRO use in pregnant women. Oral administration of repotrectinib to pregnant rats during the period of organogenesis resulted in fetal malformations at doses approximately 0.3 times the recommended dose of 160 mg twice daily based on BSA *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Published reports of individuals with congenital mutations in TRK pathway proteins suggest that decreases in TRK-mediated signaling are correlated with obesity, developmental delays, cognitive impairment, insensitivity to pain, and anhidrosis.

Animal Data

In an embryo-fetal development study, once daily oral administration of repotrectinib to pregnant rats during the period of organogenesis from gestation day 6 to 17 resulted in maternal effects of increased body weight and skin abrasions/ulcerations at doses ≥6 mg/kg, fetal malformations of malrotated hindlimbs and lower fetal body weights at doses ≥12 mg/kg [approximately 0.3 times the recommended dose of 160 mg twice daily based on BSA]. No embryolethality was observed.

8.2 Lactation

Risk Summary

There are no data on the presence of AUGTYRO in human milk or its effects on either the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children from AUGTYRO, advise a lactating woman to discontinue breastfeeding during treatment with AUGTYRO and for 10 days after the last dose.

8.3 Females and Males of Reproductive Potential

AUGTYRO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of childbearing potential prior to initiating AUGTYRO *[see Use in Specific Populations (8.1)]*.

Contraception

AUGTYRO can cause embryo-fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Females

Advise females of childbearing potential to use effective non-hormonal contraception during treatment with AUGTYRO and for 2 months following the last dose. AUGTYRO can render some hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Males

Based on genotoxicity findings, advise male patients with female partners of childbearing potential to use effective contraception during treatment with AUGTYRO and for 4 months following the last dose *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of AUGTYRO in pediatric patients with *ROS1*-positive NSCLC has not been established.

Juvenile Animal Data

Daily oral administration of repotrectinib to juvenile rats for 8 weeks starting on postnatal day 12 (approximately equal to a human pediatric age of a newborn) resulted in toxicities similar to those observed in adult rats, though juvenile animals showed decreased body weight gain at doses ≥1

mg/kg (approximately ≥0.04 times the human exposure based on AUC at the recommended clinical dose of 160 mg BID) and decreased femur lengths at 3 mg/kg (approximately 0.1 times the human exposure based on AUC at the recommended clinical dose of 160 mg BID). Decreased body weight gain and decreased femur lengths persisted following 4 weeks of recovery.

8.5 Geriatric Use

Of the 351 patients who received AUGTYRO, 21% were 65 to 75 years old, and 7% were 75 years of age or older. There were no clinically meaningful differences in safety and efficacy between patients younger than 65 years of age and patients 65 years of age or older.

8.6 Renal Impairment

The recommended dosage of AUGTYRO has not been established in patients with severe renal impairment or kidney failure (eGFR-MDRD <30 mL/min) and patients on dialysis *[see Clinical Pharmacology (12.3)]*.

No dosage modification is recommended for patients with mild or moderate renal impairment (eGFR-MDRD 30 to 90 mL/min).

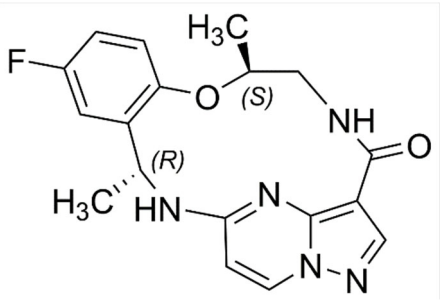
8.7 Hepatic Impairment

The recommended dosage of AUGTYRO has not been established in patients with moderate (total bilirubin >1.5 to 3 times upper limit of normal [ULN] with any AST) or severe (total bilirubin >3 times ULN with any AST) hepatic impairment *[see Clinical Pharmacology (12.3)]*.

No dosage modification is recommended for patients with mild (total bilirubin >1 to 1.5 times ULN or AST > ULN) hepatic impairment.

11 DESCRIPTION

Repotrectinib is a kinase inhibitor. The molecular formula for repotrectinib is $C_{18}H_{18}FN_5O_2$ and the molecular weight is 355.37 Daltons. The chemical name is (3R,11S)-6-Fluoro-3,11-dimethyl-10-oxa-2,13,17,18,21-pentaazatetracyclo[13.5.2.0^{4,9}.0^{18,22}]docosa-1(21),4,6,8,15(22),16,19-heptaen-14-one. The chemical structure of repotrectinib is as follows:



Repotrectinib is a white to off-white powder.

AUGTYRO (repotrectinib) capsules for oral use are supplied as printed hard shell capsules containing 40 mg of repotrectinib. Inactive ingredients are microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium, and colloidal silicon dioxide.

The white opaque capsule shell contains gelatin and titanium dioxide. The printing ink contains shellac and FD & C blue #2 aluminum lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 that include ROS1 domains can drive tumorigenic potential through hyperactivation of downstream signaling pathways leading to unconstrained cell proliferation. Repotrectinib exhibited anti-tumor activity in cultured cells expressing *ROS1* fusions and mutations including *SDC4-ROS1*, *SDC4-ROS1*^{G2032R}, *CD74-ROS1*, *CD74-ROS1*^{G2032R}, *CD74-ROS1*^{D2033N}, and *CD74-ROS1*^{L2026M}.

12.2 Pharmacodynamics

Repotrectinib exposure-response relationships and the time course of pharmacodynamic responses are not fully characterized.

Cardiac Electrophysiology

AUGTYRO does not cause a mean increase in the QTc interval > 20 milliseconds (ms) at 160 mg QD followed by 160 mg BID, the approved recommended dosage.

12.3 Pharmacokinetics

The geometric mean (CV%) of repotrectinib steady state peak concentration ($C_{max,ss}$) is 713 (32.5%) ng/mL and the area under the time concentration curve ($AUC_{0-24h,ss}$) is 7210 (40.1%) ng•h/mL following the approved recommended twice daily dosage in patients with cancer. Repotrectinib C_{max} and AUC_{0-inf} increases approximately dose proportional (but less than linear with estimated slopes of 0.78 and 0.70, respectively) over the single dose range of 40 mg to 240 mg (0.25 to 1.5 times the approved recommended dosage). Steady state PK was time-dependent with an autoinduction of CYP3A4. Steady state is achieved within 14 days of daily administration of 160 mg.

Absorption

The geometric mean (CV%) absolute bioavailability of repotrectinib is 45.7% (19.6%). Peak repotrectinib concentration occurred at approximately 2 to 3 hours post a single oral dose of 40 mg to 240 mg (0.25 to 1.5 times the approved recommended dosage) under fasted conditions.

Effect of Food

No clinically significant differences in repotrectinib pharmacokinetics were observed in patients with cancer following administration of a high-fat meal (approximately 800-1000 calories, 50% fat).

Distribution

The geometric mean (CV%) apparent volume of distribution (Vz/F) was 432 L (55.9 %) in patients with cancer following a single 160 mg oral dose of AUGTYRO.

AUGTYRO binding to plasma protein was 95.4% in vitro. The blood-to-plasma ratio was 0.56 in vitro.

Elimination

Repotrectinib elimination is time-dependent due to autoinduction of CYP3A4.

The repotrectinib mean terminal half-life is approximately 50.6 h for patients with cancer following a single dose. The steady state repotrectinib terminal half-life is approximately 35.4 h for patients with cancer.

The geometric mean (CV%) apparent oral clearance (CL/F) was 15.9 L/h (45.5%) in patients with cancer following a single 160 mg oral dose of AUGTYRO.

Metabolism

Repotrectinib is primarily metabolized by CYP3A4 followed by secondary glucuronidation.

Excretion

Following a single oral 160 mg dose of radiolabeled repotrectinib, 4.84% (0.56% as unchanged) was recovered in urine and 88.8% (50.6% unchanged) in feces.

Specific Populations

No clinically significant differences in the pharmacokinetics of repotrectinib were observed based on age (18 to 84 years), sex, race/ethnicity (Caucasian 54%, Asian 38%, Black 7%), mild to moderate renal impairment (eGFR 30 to < 90 mL/min), or mild hepatic impairment (total bilirubin >1 to 1.5 times ULN or AST > ULN). The effect of moderate (total bilirubin >1.5 to 3 times ULN with any AST) or severe (total bilirubin >3 x ULN with any AST) hepatic impairment, severe renal impairment, kidney failure (eGFR < 30 mL/min), or dialysis on repotrectinib pharmacokinetics is unknown or not fully characterized.

Drug Interaction Studies

Clinical Studies

Strong CYP3A and P-gp inhibitors: Repotrectinib $AUC_{0\text{-}inf}$ increased by 5.9-fold and C_{max} by 1.7-fold following concomitant use with itraconazole (strong CYP3A and P-gp inhibitor).

Strong CYP3A and P-gp inducers: Repotrectinib $AUC_{0\text{-}inf}$ decreased by 92% and C_{max} by 79% following concomitant use with rifampin (strong CYP3A and P-gp inducer).

CYP3A substrates: Midazolam (CYP3A substrate $AUC_{0\text{-}inf}$ decreased by 69% and C_{max} by 48% following concomitant use in subjects who were previously administered 160 mg repotrectinib once daily for 14 days followed by 160 mg twice daily for 7 days.

In vitro Studies

CYP Enzymes: Repotrectinib induces CYP3A4, CYP2B6, CYP2C8, CYP2C19, CYP2C9 and inhibits CYP3A4/5 (GI tract). Repotrectinib does not induce CYP1A2.

Other Metabolic Pathways: Repotrectinib inhibits UGT1A1.

Transporter Systems: Repotrectinib inhibits P-gp, BCRP, OATP1B1, and MATE2-K. Repotrectinib is a substrate for P-gp.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with repotrectinib were not conducted.

Repotrectinib was genotoxic in an in vitro assay in human lymphoblastoid TK6 cells and in an in vivo rat bone marrow micronucleus assay via an aneugenic mechanism of action. Repotrectinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay.

Dedicated fertility studies were not conducted with repotrectinib. There were no effects on male and female reproductive organs observed in general repeat-dose toxicology studies of up to 3 months in duration in rats and monkeys at any dose level tested, which equated to exposures of up to approximately 3 times the human exposure at the 160 mg twice daily dose based on AUC.

14 CLINICAL STUDIES

14.1 Locally Advanced or Metastatic *ROS1*-Positive NSCLC

The efficacy of AUGTYRO was evaluated in TRIDENT-1, a multicenter, single-arm, open-label, multi-cohort clinical trial (NCT03093116). Eligible patients were required to have *ROS1*-positive locally advanced or metastatic NSCLC, ECOG performance status ≤1, measurable disease per RECIST v 1.1, and ≥8 months from first dose. All patients were assessed for CNS lesions at baseline, and patients with symptomatic brain metastases were excluded from the trial. Patients received AUGTYRO 160 mg orally once daily for 14 days, then increased to 160 mg twice daily until disease progression or unacceptable toxicity. Tumor assessments were performed at least every 8 weeks. Identification of *ROS1* gene fusions in tumor specimens was prospectively determined in local laboratories using next-generation sequencing (NGS), polymerase chain reaction (PCR) or fluorescence in situ hybridization (FISH) tests. All *ROS1*-positive patients by local FISH testing required central laboratory confirmation of *ROS1* fusion using an analytically validated NGS test. *ROS1* fusions were identified by NGS in 51%, FISH in 26%, and PCR in 23%. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) according to RECIST v1.1 as assessed by blinded independent central review (BICR). Intracranial response according to modified RECIST v1.1 was assessed by BICR. Tumor assessments with imaging were performed every 8 weeks. The efficacy populations included 71 ROS1 TKI-naïve patients who received up to 1 prior line of platinum-based chemotherapy and/or immunotherapy and 56 patients who received 1 prior ROS1 TKI with no prior platinum-based chemotherapy or immunotherapy.

Among the 71 ROS1 TKI-naïve patients, the median age was 57 years (range: 28 to 80); female (60.6%); Asian (67.6%), White (25.4%), Hispanic or Latino (4.2%), Black or African American (1.4%); never smoked (63.4%); and ECOG performance status of 1 at baseline (66.2%). At baseline, 94.4% of patients had metastatic disease, 25.4% of patients had CNS metastases by BICR; 97.2% had adenocarcinoma; and 28.2% patients 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 (including crizotinib [82%] and entrectinib [16%]) with no prior platinum-based chemotherapy or immunotherapy, the median age was 57 years (range: 33 – 78); female (67.9%); Asian (48.2%), White (44.6%), Black or African American and Hispanic or Latino (1.8% each); never smoked (64.3%); and ECOG performance status of 1 at baseline (67.9%). At baseline, 98.2% patients had metastatic disease, 42.9% with CNS metastases by BICR, and 94.6% had adenocarcinoma.

Efficacy results are summarized in Table 5.

Table 5: Efficacy Results for Patients with *ROS1*-Positive NSCLC in TRIDENT-1

Efficacy Parameters	ROS1 Inhibitor Naïve Patients (N=71)	ROS1 Inhibitor Pretreated Patients (N=56)
Confirmed Overall Response Rate, % (95% CI)	79% (68, 88)	38% (25, 52)
Complete Response	6%	5%
Partial Response	73%	32%
Duration of Response (DOR)[a]		
Median in Months (95% CI)[b]	34.1 (25.6, NE)	14.8 (7.6, NE)
Range (months)	1.4+, 42.4+	3.6, 22.9+
% DOR ≥12 months[c]	70	48

Abbreviations: CI = confidence interval; NE = not evaluable; "+" indicates ongoing response

[a] DOR results are based on the updated data as of 19 December 2022.

[b] Median DOR (95% CI) are based on Kaplan-Meier estimates.

[c] DOR landmark analysis is based on the observed DOR.

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).

16 HOW SUPPLIED/STORAGE AND HANDLING

AUGTYRO (repotrectinib) 40 mg, Size 0, white opaque cap, white opaque body, hard shell capsules, filled with a white to off-white powder which may appear as a plug, imprinted with "REP 40" in blue text on the cap are supplied as follows:

- Bottles of 60 capsules (NDC 0003-4040-60)
- Bottles of 120 capsules (NDC 0003-4040-12)

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) *[See USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

Central Nervous System (CNS) Effects

- Advise patients to inform their healthcare provider if they experience new or worsening CNS symptoms. Instruct patients not to drive or operate hazardous machinery if they are experiencing CNS adverse reactions *[see Warnings and Precautions (5.1)]*.

Interstitial Lung Disease (ILD)/Pneumonitis

- Advise patients to inform their healthcare provider if they experience new or worsening pulmonary symptoms indicative of ILD/pneumonitis *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

- Advise patients of the need for laboratory tests to monitor liver function and to immediately report symptoms of hepatotoxicity *[see Warnings and Precautions (5.3)]*.

Myalgia with Creatinine Phosphokinase Elevation

- Advise patients to inform their healthcare provider if they experience muscle pain *[see Warnings and Precautions (5.4)]*.

Hyperuricemia

- Advise patients to inform their healthcare provider if they experience signs or symptoms associated with hyperuricemia *[see Warnings and Precautions (5.5)]*.

Skeletal Fractures

- Inform patients that bone fractures have occurred in patients taking AUGTYRO and advise patients to report symptoms to their healthcare provider *[see Warnings and Precautions (5.6)]*.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1, 8.3)]*.
- Advise females of reproductive potential to use effective non-hormonal contraception during treatment with AUGTYRO and for 2 months after the last dose, since AUGTYRO can render some hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.
- 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 *[see Use in Specific Populations (8.1, 8.3)]*.

Lactation

- Advise females not to breastfeed during treatment with AUGTYRO and for 10 days after the last dose *[see Use in Specific Populations (8.2)]*.

Drug Interactions

- Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions (7)]*.
- Advise patients to avoid grapefruit or grapefruit juice while taking AUGTYRO *[see Drug Interactions (7)]*.
- Advise patients that hormonal contraceptives can be ineffective while taking AUGTYRO *[see Drug Interactions (7)]*.

Administration

- Advise patients to swallow AUGTYRO capsules whole with or without food *[see Dosage and Administration (2.6), Pharmacokinetics (12.3)]*.
- Instruct patients if they miss a dose, or vomit at any time after taking a dose of AUGTYRO, not to "make it up," but take the next dose of AUGTYRO at the next scheduled time *[see Dosage and Administration (2.6)]*.

For more information, go to www.AUGTYRO.com or call 1-877-284-8976.

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PATIENT INFORMATION
AUGTYRO™ [Aug-TYE-ro]
(repotrectinib)
capsules

What is the most important information I should know about AUGTYRO?

AUGTYRO may cause serious side effects, including:

- **Central nervous system (CNS) effects.** Tell your healthcare provider right away if you experience any new or worsening symptoms of CNS effects during treatment with AUGTYRO, including:
  - dizziness
  - vertigo
  - changes in mood, such as anxiety, irritability, and depression
  - balance or coordination problems
  - problems with thinking, such as forgetfulness or confusion
  - seeing or hearing things that are not real (hallucinations)
  - problems with concentration, attention, memory, and sleep
- **Lung problems (pneumonitis).** Tell your healthcare provider if you have any new or worsening symptoms of lung problems, including a dry cough (without mucus), productive cough (with mucus), wheezing, or trouble breathing.
- **Liver problems.** Your healthcare provider will do blood tests to check your liver function before starting and during treatment with AUGTYRO. Tell your healthcare provider right away if you develop symptoms of liver problems including:
  - your skin or the white part of your eyes turns yellow
  - dark or "tea-colored" urine
  - light-colored stools (bowel movements)
  - loss of appetite
  - nausea or vomiting
  - pain on the upper right side of your stomach area
- **Muscle problems.** Your healthcare provider will do blood tests before starting treatment with AUGTYRO, at least every 2 weeks for the first month and as needed during treatment. Tell your healthcare provider right away if you get new or worsening signs and symptoms of muscle problems, including unexplained muscle pain or muscle pain that does not go away, tenderness, or weakness.
- **Increased uric acid level in your blood (hyperuricemia).** AUGTYRO may cause an excess of uric acid in your blood. Your healthcare provider will do tests before and during your treatment with AUGTYRO to check the uric acid level in your blood. Your healthcare provider may prescribe medications if you have high blood uric acid levels. Tell your healthcare provider if you experience symptoms of increased uric acid including:
  - red, hot, tender, or swollen joints, especially in your big toe
  - pain in your stomach-area or sides
  - decrease in your amount of urine or no urine at all
  - nausea or vomiting
  - pink or brown urine or blood in your urine
- **Bone fractures.** AUGTYRO may increase your risk for bone fractures. Bone fractures may happen with or without a fall or other injury. Tell your healthcare provider right way if you have pain, changes in movement, or bone abnormalities.

See **"What are the possible side effects of AUGTYRO?" for more information about side effects.**

What is AUGTYRO?

AUGTYRO is a prescription medicine used to treat adults with non-small cell lung cancer (NSCLC) that has spread within your chest or to other parts of the body and is caused by an abnormal *ROS1* gene.

It is not known if AUGTYRO is safe and effective in children.

Before taking AUGTYRO, tell your healthcare provider about all your medical conditions, including if you:

- have nervous system (neurological) problems.
- have lung or breathing problems other than lung cancer.
- have liver problems.
- are pregnant or plan to become pregnant. AUGTYRO can harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with AUGTYRO.
  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with AUGTYRO.
  - You should use effective non-hormonal birth control (contraception) during treatment and for 2 months after the last dose of AUGTYRO.
  - Birth control methods that contain hormones (such as birth control pills, injections or transdermal system patches) may not work as well during treatment with AUGTYRO.
  - Talk to your healthcare provider about birth control methods that may be right for you.

  Males with female partners who are able to become pregnant:
  - You should use effective birth control during treatment with AUGTYRO and for 4 months after the last dose.
- are breastfeeding or plan to breastfeed. It is not known if AUGTYRO passes into your breast milk. Do not breastfeed during treatment and for 10 days after the last dose of AUGTYRO. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, or herbal supplements.

How should I take AUGTYRO?

- Take AUGTYRO exactly as your healthcare provider tells you to take it. Do not change your dose or stop taking AUGTYRO unless your healthcare provider tells you to.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with AUGTYRO if you develop side effects.
- Take AUGTYRO at about the same time each day with or without food.
- Swallow AUGTYRO capsules whole with water. Do not open, crush, chew or dissolve the capsule. Do not take a capsule if it is broken, cracked, or damaged.
- If you miss a dose, or vomit at any time after taking a dose of AUGTYRO, do not take an extra dose. Just skip the dose and take your next dose at the regularly scheduled time. Do not take 2 doses at the same time to make up a missed or vomited dose.

What should I avoid while taking AUGTYRO?

- You should not drink grapefruit juice or eat grapefruit during your treatment with AUGTYRO. It may increase the amount of AUGTYRO in your blood to a harmful level.
- Do not drive or operate machinery until you know how AUGTYRO affects you. If you experience dizziness, blurred vision, memory loss, changes in mental status, confusion, hallucinations or have trouble with balance or coordination or problems with concentration and attention, do not drive or operate machinery until your symptoms have resolved.

What are the possible side effects of AUGTYRO?

AUGTYRO may cause serious side effects, including:

- See **"What is the most important information I should know about AUGTYRO?"**

The most common side effects of AUGTYRO include:

- dizziness
- change in sense of taste
- feeling of numbness or tingling in your arms or legs
- constipation
- trouble with balance, coordination, and walking
- shortness of breath
- problems with thinking, such as forgetfulness or confusion, memory problems and hallucinations
- tiredness
- nausea

These are not all the possible side effects of AUGTYRO.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AUGTYRO?

- Store AUGTYRO at room temperature between 68°F to 77°F (20°C to 25°C).

Keep AUGTYRO and all medicines out of the reach of children.

General information about the safe and effective use of AUGTYRO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AUGTYRO for a condition for which it was not prescribed. Do not give AUGTYRO to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about AUGTYRO that is written for health professionals.

What are the ingredients of AUGTYRO?

Active ingredient: repotrectinib
Inactive ingredients: microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium, and colloidal silicon dioxide. Capsule shell contains gelatin and titanium dioxide. Printing ink contains shellac and FD & C blue #2 aluminum lake.

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This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 11/2023