NDA 218213/S-001

ACCELERATED APPROVAL

Bristol Myers Squibb Company
Attention: Lise Alessio, Pharm.D., M.S.
Associate Director, Global Regulatory Strategy & Policy
P.O. Box 5326
Princeton, NJ 08543

Dear Dr. Alessio:

Please refer to your supplemental new drug application (sNDA) received December 15, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Augtyro (repotrectinib) capsules, for oral use.

This "Prior Approval" sNDA proposes to add a new indication for Augtyro:

AUGTYRO is indicated for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that:

- have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion,
- are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and
- have progressed following treatment or have no satisfactory alternative therapy.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 314.510, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the accelerated approval statutory provisions and regulations.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 314.510 you are required to conduct further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If required postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement(s) specified in your submission dated June 10, 2024. These requirements are listed below.

4649-1 Conduct an analysis of patients from ongoing or planned trials intended to verify and describe the clinical benefit of repotrectinib through more precise estimation of the overall response rate and mature response duration per independent review assessment, in adult and pediatric patients 12 years of age and older with solid tumors with a neurotrophic receptor tyrosine kinase (NTRK) gene fusion who have locally advanced or metastatic disease or would require surgical resection that would result

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

in severe morbidity; and have no satisfactory alternative treatment or that have progressed following treatment.

A sufficient number of patients will be evaluated to more precisely characterize response and durability of response for a spectrum of patients with different TKI-naïve and TKI-pretreated tumor types. All responding patients will be followed for at least 12 months from the onset of response or until disease progression whichever comes first.

The timetable you submitted on June 10, 2024, states that you will conduct this trial according to the following schedule:

Trial Completion: 11/2029
Final Report Submission: 05/2030

4649-2 Complete the analysis of the 23 responding patients in the efficacy evaluable population of 40 TKI-naïve patients and the 24 responding patients in the efficacy evaluable population of 48 TKI-pretreated patients in the TRIDENT-1 trial intended to verify and describe the clinical benefit and further characterize the duration of response in patients who achieved a complete or partial response to repotrectinib. All responding patients will be followed for at least 2 years from the onset of response or until disease progression, whichever comes first. Duration of response will be assessed by independent central review.

The timetable you submitted on June 10, 2024, states that you will conduct this trial according to the following schedule:

Trial Completion: 09/2024
Final Report Submission: 03/2025

Submit clinical protocols to your IND 130465 for this product. FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

You must submit reports of the progress of each clinical trial required under section 506(c) (listed above) to this NDA approximately every 180 days (see section 506B(a)(2) of the FDCA) (hereinafter “180-day reports”).

You are required to submit two 180-day reports per year for each open study or clinical trial required under section 506(c). One report will be a standalone submission and the other report will be combined with your application’s annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 314.81(b)(2). The standalone 180-

day report will be due 180 days after the date of approval of the original NDA (with a 60-day grace period). Submit the other 180-day report with your application's ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted.[3] Depending on the date of approval of the original application, you may be required to submit a 180-day report shortly after receipt of this letter.

Your 180-day reports must include the information listed in 21 CFR 314.81(b)(2)(vii)(a). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[4]

180-day reports must be clearly designated "**NDA 218213/S-001 180-Day AA PMR Progress Report**."

FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 314.81(b)(2), in addition to the submission of reports 180 days after the date of approval of the original NDA each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

Submit final reports to this NDA as a supplemental application. For administrative purposes, the cover page of all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

[3] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.

[4] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of skeletal fractures or assess a signal of serious risks of long-term effects on growth, neurological outcomes, and development in pediatric patients.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of skeletal fractures or assess the signal of serious risks of long-term effects on growth, neurological outcomes, and development in pediatric patients.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4649-3 Conduct integrated safety analyses from an adequate number of patients enrolled in clinical trial(s) designed to characterize the known serious risk of fractures and sequelae of fractures in patients exposed to repotrectinib with reasonable precision; to identify risk factors for development of these sequelae; and to identify mitigating measures for the risk of skeletal fractures. Include sufficient bone monitoring to achieve these objectives including but not limited to initial and serial assessment of bone mineral density (BMD) with dual x-ray absorptiometry (DXA) scans, and markers of bone formation, bone resorption, and calcium metabolism.

The timetable you submitted on June 10, 2024, states that you will conduct this trial according to the following schedule:

Trial Completion:	05/2029
Final Report Submission:	11/2029

4649-4 Conduct a clinical trial or analysis of clinical trials of repotrectinib in a sufficient number of pediatric patients 12 years of age and older with NTRK-fusion positive solid tumors to evaluate the potential serious risk of adverse long-term effects of repotrectinib on growth and development and neurological outcomes, with reasonable precision. Patients will be monitored for growth and developmental milestones using age-appropriate screening tools and undergo neurological examination at appropriate

intervals. Evaluations will include neurological exams with neurocognitive assessment, Karnofsky/Lansky score, growth as measured by height, weight, height velocity, and height standard deviation scores (SDS), age at adrenarche if applicable (males), age at menarche if applicable (females) and Tanner Stage. Patient monitoring will be performed until discontinuation of study treatment or a minimum of 5 years from start of treatment, whichever occurs first.

The timetable you submitted on June 10, 2024, states that you will conduct this trial according to the following schedule:

Trial Completion:	11/2029
Final Report Submission:	05/2030

Submit clinical protocol(s) to your IND 130465 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4649-5 Complete an appropriate clinical validation study using clinical trial data to establish and support the availability of an in vitro diagnostic device that is essential to the safe and effective use of repotrectinib for patients with solid tumors that carry NTRK1/2/3 gene fusions.

The timetable you submitted on June 10, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2025

Submit clinical protocols to your IND 130465 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, email Autumn Zack-Taylor, M.S., Senior Regulatory Health Project Manager, at Autumn.Zack-Taylor@fda.hhs.gov**.**

Sincerely,

{See appended electronic signature page}

Steven Lemery, M.D., M.H.S.
Director
Division of Oncology 3
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

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

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.2)	06/2024
Dosage and Administration (2.1)	06/2024
Warnings and Precautions (5.6)	06/2024

----------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). (1.1)
- adult and pediatric patients 12 years of age and older with solid tumors that:
  - have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion and
  - are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity.
  - have progressed following treatment or have no satisfactory alternative therapy.

  This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.2)

----------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)
- Select patients for treatment of locally advanced or metastatic solid tumors based on the presence of an *NTRK* gene fusion. (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, 160 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, fatigue, ataxia, cognitive impairment, muscular weakness, and nausea. (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: 06/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 *ROS1*-Positive Non-Small Cell Lung Cancer

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)]*.

1.2 *NTRK* Gene Fusion-Positive Solid Tumors

AUGTYRO is indicated for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that:

- have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion *[see Dosage and Administration (2.1)]*,
- are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and
- have progressed following treatment or have no satisfactory alternative therapy.

This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

NSCLC

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.

Solid Tumors

Select patients for the treatment of solid tumors with AUGTYRO based on the presence of *NTRK1/2/3* rearrangements in tumor specimens *[see Clinical Studies (14.2)]*. An FDA-approved test to detect *NTRK1/2/3* rearrangements for selecting patients for treatment with AUGTYRO is not currently available.

- In patients with secretory breast cancer or mammary analogue secretory cancer, consider treatment without confirmation of *NTRK* rearrangements in tumor specimens.

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 for adult and pediatric patients 12 years of age and older 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.

Capsules: 160 mg, blue, opaque, immediate release, Size 0, hard shell capsule, filled with white to off-white powder which may appear as a plug, imprinted with “REP 160” in white 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 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% of patients.

Dizziness, including vertigo, occurred in 65% of patients; 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% of patients. 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.

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% patients permanently discontinued AUGTYRO due to cognitive adverse reactions.

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% of patients 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% 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 426 patients treated with AUGTYRO, ILD/pneumonitis (pneumonitis [2.8%] and ILD [0.2%]) occurred in 3.1% of patients; Grade 3 ILD/pneumonitis occurred in 1.2% 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, 0.5% 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 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 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 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 the same or reduced dose upon improvement *[see Dosage and Administration (2.5)]*.

5.5 Hyperuricemia

AUGTYRO can cause hyperuricemia.

Among the 426 patients treated with AUGTYRO, 21 patients (5%) experienced hyperuricemia reported as an adverse reaction and 0.7% 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 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 *[see Pediatric Use (8.4)]*.

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 and below reflects exposure to AUGTYRO in 426 patients with *ROS1*-positive NSCLC (n=320), *NTRK1/2/3*-positive solid tumors (n=104), or other solid tumors (n=2) in TRIDENT-1. 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 *[see Clinical Studies (14.1, (14.2)]*. 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. Forty-eight percent of patients were exposed to AUGTYRO for at least 6 months, and 28% were exposed for greater than 1 year.

The median age of patients who received AUGTYRO was 57 years (range: 18 to 93); 59% female; 43% White, 47% Asian, 2.8% Black, 0.5% Native Hawaiian or Other Pacific Islander, 0.5% American Indian or Alaska Native, 6.1% race not reported or other, and 0.7% unknown.

Serious adverse reactions occurred in 35% of patients who received AUGTYRO. Serious adverse reactions in ≥2% of patients included pneumonia (6.3%), dyspnea (3.1%), pleural effusion (2.8%), and hypoxia (2.6%). Fatal adverse reactions occurred in 3.5% of patients who received AUGTYRO, including pneumonia, pneumonia aspiration, cardiac arrest, sudden cardiac death, cardiac failure, hypoxia, dyspnea, respiratory failure, tremor, and disseminated intravascular coagulation.

Permanent discontinuation of AUGTYRO due to an adverse reaction occurred in 7% of patients. There were no specific adverse reactions that accounted for ≥1% of permanent discontinuations.

Dosage interruptions of AUGTYRO due to an adverse reaction occurred in 50% of patients. Adverse reactions that required dosage interruption in ≥2% of patients were dizziness, dyspnea, muscular weakness, ataxia, pneumonia, peripheral neuropathy, anemia, and vomiting.

Dose reductions of AUGTYRO due to an adverse reaction occurred in 38% of patients. Adverse reactions that required dosage reductions in ≥2% of patients included dizziness, ataxia, muscular weakness, peripheral neuropathy, and cognitive impairment.

The most common (≥20%) adverse reactions that occurred in patients receiving AUGTYRO were dizziness, dysgeusia, peripheral neuropathy, constipation, dyspnea, fatigue, ataxia, cognitive impairment, muscular weakness and nausea.

Table 3 summarizes the adverse reactions that occurred in TRIDENT-1.

Table 3: Adverse Reactions (≥10%) in Patients with *ROS1*-Positive NSCLC or *NTRK*-Positive Solid Tumors Who Received AUGTYRO in TRIDENT-1

Adverse Reaction[1]	AUGTYRO N=426	
	All Grades (%)	Grade 3 or 4 (%)
Nervous System Disorders		
Dizziness[a]	65	2.8
Dysgeusia[b]	54	0
Peripheral neuropathy[c]	49	1.4
Ataxia[d]	28	0.5
Cognitive impairment[e]	25	0.9
Headache[f]	19	0
Gastrointestinal Disorders		
Constipation	38	0.2
Nausea	20	0.7
Diarrhea	14	0.7
Vomiting	12	1.2
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea[g]	30	6
Cough[h]	18	0.2
Pneumonia[i]	11	6
General Disorders		
Fatigue[j]	30	1.2
Edema[k]	15	0.5
Decreased appetite	11	0.2
Musculoskeletal and Connective Tissue Disorders		
Muscular weakness	20	2
Myalgia[l]	13	0.7
Metabolism and Nutritional		
Increased weight	16	3
Eye Disorders		
Vision disorders[m]	12	0.5

[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 and coordination abnormal

[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 pneumonia, pneumonia aspiration, lower respiratory tract infection, pneumonia viral, pneumonia bacterial, lower respiratory tract infection bacterial, pneumonia klebsiella
[j] Includes terms fatigue and asthenia
[k] Includes terms generalized edema, periorbital edema, localized edema, face edema, edema peripheral, edema, eye edema, scrotal edema
[l] Includes terms myalgia, myositis, musculoskeletal discomfort, musculoskeletal pain
[m] 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 occurring in <10% of patients receiving AUGTYRO were pyrexia (9.2%) and fall (3.8%).

Table 4 summarizes the laboratory abnormalities in TRIDENT-1.

Table 4: Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with *ROS1*-Positive NSCLC or *NTRK*-Positive Solid Tumors Who Received AUGTYRO in TRIDENT-1

Laboratory Abnormality[1]	**AUGTYRO[2] N=426**	
	All Grades (%)	**Grade 3 or 4 (%)**
Hematology		
Decreased hemoglobin	79	8.4
Decreased lymphocytes	43	10
Decreased neutrophils	34	9
Increased activated partial thromboplastin time	26	0.3
Increased INR	24	0
Chemistry		
Increased creatine phosphokinase	61	7
Increased gamma glutamyl transferase	50	13
Increased aspartate aminotransferase	41	2.9
Increased alanine aminotransferase	38	3.3
Increased sodium	33	0.2
Increased alkaline phosphatase	29	2.1
Increased glucose	26	2.4
Increased urate	23	12
Decreased phosphate	22	6
Increased potassium	22	0.7
Decreased glucose	20	0.2

[1] Based on NCI CTCAE v4.03
[2] The denominator used to calculate the rate varied from 233 to 423 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 of reproductive potential to use an effective nonhormonal contraceptive *[see Use in Specific Populations (8.1, 8.3)]*.

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 have not been established.

The safety and effectiveness of AUGTYRO have not been established in pediatric patients younger than 12 years of age with solid tumors who have an *NTRK* gene fusion.

The safety and effectiveness of AUGTYRO for the treatment of locally advanced or metastatic *NTRK*-positive solid tumors have been established in pediatric patients 12 years of age or older. Use of AUGTYRO in this age group is supported by evidence from an adequate and well-controlled study in adult patients with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older. This includes data demonstrating that the exposure of repotrectinib in pediatric patients 12 years of age and older is expected to result in similar safety and efficacy to that of adults, and that the course of locally advanced or metastatic *NTRK*-positive solid tumors is sufficiently similar in adults and pediatric patients 12 years of age or older to allow extrapolation of data in adult to pediatric patients 12 years of age or older *[see Dosage and Administration (2.4), Warnings and Precautions (5.7), Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*.

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 426 patients who received AUGTYRO, in the TRIDENT-1 study for *ROS1*-positive non-small cell lung cancer or *NTRK* gene fusion-positive solid tumors, 19% were 65 to 75 years old, and 6% 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 <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 30 to 90 mL/min).

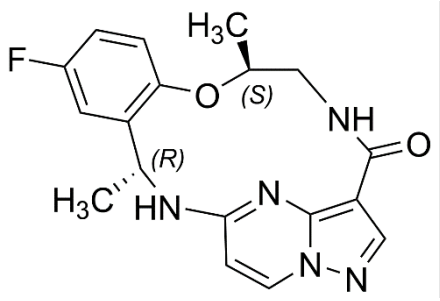
8.7 Hepatic Impairment

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.

AUGTYRO (repotrectinib) capsules for oral use are supplied as printed hard shell capsules containing 160 mg of repotrectinib. Inactive ingredients are microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium, magnesium stearate, and colloidal silicon dioxide.

The blue opaque capsule shell contains gelatin, titanium dioxide and FD & C blue #1. The printing ink contains shellac and titanium dioxide.

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 or TRK 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}. Repotrectinib also inhibited cell proliferation in cultured cells expressing *NTRK* fusions and mutations including LMNA-TRKA, LMNA-TRKA^{G595R}, EVT6-TRKB^{G639R}, and ETV6-TRKC^{G623R}.

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 60.7 h for patients with cancer following a single dose. The steady state repotrectinib terminal half-life is approximately 40.3 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 (12 to 93 years), sex, race (White 50%, 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). 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 (*ROS1*^{G2032R}), gatekeeper (*ROS1*^{L2026M}), and other mutations (*ROS1*$^{S1986F/Y}$).

14.2 Locally Advanced or Metastatic *NTRK* Gene Fusion-Positive Solid Tumors

The efficacy of AUGTYRO was evaluated in TRIDENT-1 (NCT03093116), a multi-center, single-arm, open-label, multi-cohort clinical trial in 88 adult patients with locally advanced or metastatic *NTRK* gene fusion-positive (*NTRK1/2/3*) solid tumors who had either received a prior TKI treatment or were TKI-naïve. 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 every 8 weeks. *NTRK* gene fusions were identified prospectively using NGS in 94%, FISH in 5%, and PCR in 1%. *NTRK* gene fusion-positive tumors identified by local FISH testing required central laboratory confirmation using an analytically validated NGS test. The major efficacy outcome measures were ORR and DOR according to RECIST v1.1 as assessed by BICR. Intracranial response according to modified RECIST v1.1 was assessed by BICR.

Among the 40 TRK TKI-naïve patients, the median age was 61 years (range: 25 to 84); 60% were female patients; race was Asian 53%, White 25%, Black or African American 5%, and other or not reported 18%; ethnicity was Hispanic or Latino 5%, not Hispanic or Latino 87%, and not reported 8%; and ECOG performance status of 1 at baseline was 55%. At baseline, 98% of patients had metastatic disease and 23% of patients had CNS metastases by BICR. Seventy percent (n=28) of patients received prior systemic therapy with a median of one prior systemic regimen, and 7.5% (n=3) received three or more prior systemic regimens.

Among the 48 TRK TKI-pretreated patients, the median age was 58 years (range: 20 to 81); 48% were female patients; race was White 65%, Asian 25%, Black or African American 2%, and not reported 8%; ethnicity was not Hispanic or Latino 92%, and missing 8%; and ECOG performance status of 1 at baseline was 60%. At baseline, 96% of patients had metastatic disease and 25% of patients had CNS metastases by BICR. Seventy-seven percent (n=37) of patients received 2 or more prior systemic regimens, and 46% (n=22) received three or more prior systemic regimens, and 7 patients (15%) received 2 prior TKI therapies.

Efficacy results are summarized in Table 6.

Table 6: Efficacy Results for Patients with *NTRK* Gene Fusion-Positive Tumors in TRIDENT-1

Efficacy Parameters	**TKI-Naïve Patients (n=40)**	**TKI-Pretreated Patients (n=48)**
Confirmed Overall Response Rate, % (95% CI)	58 (41, 73)	50 (35, 65)
Complete Response, %	15	0
Partial Response, %	43	50
Median Duration of Response (mDOR)[a], in Months (95% CI)	NE (NE, NE)	9.9 (7.4, 13.0)
Range (months)	3.7+, 43.9+	1.8, 26.5+
% with DOR $\geq$ 6 months[b]	87	71
% with DOR $\geq$ 9 months[b]	83	63

% with DOR ≥ 12 months[b]	83	42

NE = not evaluable; "+" indicates ongoing response

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

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

Among the 88 patients, 5 had measurable CNS metastases at baseline as assessed by BICR. Responses were seen in 2 (100%) TKI-naïve patients and 3 (100%) TKI-pretreated patients. One out of 2 TKI-naïve and 2 out of 3 TKI-pretreated patients received prior radiotherapy to the brain, all more than 2 months prior to study entry.

Twenty-six of the TRK TKI-pretreated patients had a resistance mutation at baseline, including 24 with solvent front mutations (*NTRK1*^{G595R} and *NTRK3*$^{G623L/R/E/V}$ mutations), one with both a solvent front mutation and a gatekeeper mutation (*NTRK1*^{F589L}), and one with another mutation (*NTRK1*^{G667C}). In the 25 TKI-pretreated patients with solvent front mutations at baseline, ORR was 60% (95% CI: 39, 79).

ORR and DOR by tumor type in adult patients with *NTRK* gene fusion-positive solid tumors are presented in Tables 7 and 8 below.

Table 7: Efficacy Results by Tumor Type in TKI-naïve *NTRK* Gene Fusion Patients

Tumor type	**Patients (n=40)**	**ORR**		**DOR**
		n (%)	**95% CI**	**Range (months)**
NSCLC	21	13 (62)	38, 82	3.7+, 31.3+
Thyroid Cancer	5	5 (100)	48, 100	4.7, 43.9+
Salivary Gland Cancer	3	3 (100.0)	29, 100	17.7+, 31.4+
Secretory carcinoma	1	PR	NA	23.0+
Sarcoma, Soft tissue	3	1 (33)	0.8, 91	14.7+
Breast Cancer (adenocarcinoma)	2	PD, PD	NA	NA
Other*	2	SD, SD	NA	NA
Glioblastoma	1	SD	NA	NA
Cholangiocarcinoma	1	PD	NA	NA
Colorectal cancer	1	SD	NA	NA
Peripheral Nerve Sheath Tumor	1	PR	NA	23.0+

* Includes esophageal cancer and head and neck cancer

PD: progressive disease; PR: partial response; SD: stable disease; NA: not applicable

"+" indicates ongoing response

Table 8: Efficacy Results by Tumor Type in TKI-pretreated *NTRK* Gene Fusion-Positive Patients

Tumor type	**Patients (n=48)**	**ORR**		**DOR**
		n (%)	**95% CI**	**Range (months)**
NSCLC	14	6 (43)	18, 71	1.9, 23.0+
Salivary Gland Cancer	8	7 (88)	47, 100	3.7, 26.5+
Secretory carcinoma	3	3 (100)	29, 100	7.9, 26.5+
Sarcoma, Soft tissue	6	1 (17)	0.4, 64	5.6
Thyroid Cancer	4	2 (50)	7, 93	2.0, 9.6
Glioblastoma	3	1 (33.3)	0.8, 91	23.5
Cholangiocarcinoma	2	PR, PD	NA	1.8

Tumor type	Patients (n=48)	ORR		DOR
		n (%)	95% CI	Range (months)
Colorectal cancer	2	PR, SD	NA	17.5
Peripheral Nerve Sheath Tumor	2	PR, PR	NA	5.5, 11.1
Neuroendocrine Tumor	2	PR, PR	NA	5.5, 9.1
Pancreatic Cancer	2	PD, PD	NA	NA
Other*	2	SD, PD	NA	NA
Breast Cancer (adenocarcinoma)	1	PR	NA	15.6+

* Includes gallbladder cancer and unknown primary cancer
PD: progressive disease; PR: partial response; SD: stable disease; NA: not applicable
"+" indicates ongoing response

ORR and DOR in adult patients are presented by *NTRK* gene fusion partner Tables 9 and 10 below.

Table 9: Efficacy Results by *NTRK* Gene Fusion Partner in TRK TKI-Naïve Patients

***NTRK* Partner**	**Subjects (n=40)**	**ORR**		**DOR**
		n (%)	**95% CI**	**Range (Months)**
ETV6-NTRK3	12	9 (75)	(43, 95)	4.7, 31.4+
TPM3-NTRK1	7	5 (71)	(29, 96)	3.8, 23.1+
EML4-NTRK3	2	Missing, PR	NA	14.8+
IRF2BP2-NTRK1	2	PR, PR	NA	3.7+, 20.3+
PEAR1-NTRK1	2	Missing, PD	NA	NA
Unknown	2	PD, SD	NA	NA
ATP2B2-IT2-NTRK1	1	SD	NA	NA
GOLGB1-NTRK1	1	SD	NA	NA
IL1RL2-NTRK2	1	SD	NA	NA
LRPPRC-NTRK3	1	SD	NA	NA
LRRC71-NTRK1	1	Missing	NA	NA
Multiple	1	PR	NA	28.6+
RBPMS-NTRK3	1	PR	NA	34.3+
SLC28A3-NTRK2	1	PD	NA	NA
SQSTM1-NTRK1	1	PR	NA	15.7+
STRN3-NTRK1	1	PR	NA	23.9+
TMED3-NTRK3	1	PD	NA	NA
TPR-NTRK1	1	PR	NA	43.9+
TRIM33-NTRK1	1	CR	NA	17.8+

PD: progressive disease; PR: partial response; SD: stable disease; NA: not applicable
"+" indicates ongoing response

Table 10: Efficacy Results by *NTRK* Gene Fusion Partner in TRK TKI-Pretreated Subjects

***NTRK* Partner**	**Subjects (n=48)**	**ORR**		**DOR**
		n (%)	**95% CI**	**Range (Months)**
ETV6-NTRK3	24	16 (67)	(45, 84)	1.8, 26.5+
EML4-NTRK3	5	4 (80)	(28, 99)	1.9, 12.9
LMNA-NTRK1	4	1 (25)	(0.6, 81)	5.6
TPM3-NTRK1	3	0 (0)	(0, 71)	NA

ATP1B1-NTRK1	1	PD	NA	NA
BCR-NTRK2	1	SD	NA	NA
ETV6-NTRK2	1	NE	NA	NA
GP2-NTRK1	1	PD	NA	NA
IRF2BP2-NTRK1	1	Missing	NA	NA
KANK2-NTRK2	1	PR	NA	23.5
Multiple	1	PD	NA	NA
PRDX1-NTRK1	1	Missing	NA	NA
RBPMS-NTRK3	1	PD	NA	NA
SEL1L-NTRK1	1	PD	NA	NA
SQSTM1-NTRK3	1	PR	NA	5.5
STRN3-NTRK3	1	PR	NA	11.1

PR = partial response; PD = progressive disease; SD = stable disease; NA = not applicable; NE = not evaluable
"+" indicates ongoing response

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)

AUGTYRO (repotrectinib) 160 mg, Size 0, blue opaque cap, blue opaque body, hard shell capsules, filled with a white to off-white powder which may appear as a plug, imprinted with "REP 160" in white text on the cap are supplied as follows:

- Bottles of 14 capsules (NDC 0003-4160-14)
- Bottles of 60 capsules (NDC 0003-4160-60)

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 Creatine 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 treatment with AUGTYRO, every 2 weeks for the first month and as needed during treatment. 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, 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 medicines 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.
- adults and children 12 years of age and older with solid tumors (cancer) that:
  - are caused by certain abnormal *NTRK* genes, **and**
  - have spread to other parts of the body, or if surgery to remove your cancer is likely to cause severe complications, **and**
  - have grown or spread after other treatment or there is no satisfactory alternative treatment option.

It is not known if AUGTYRO is safe and effective in children with *ROS1*-positive NSCLC or in children younger than 12 years of age with *NTRK*-positive solid tumors.

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 or kidney 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.

Taking AUGTYRO with certain other medicines may affect the amount of AUGTYRO or other medicines in your blood and may cause side effects or affect the way that AUGTYRO or other medicines work. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

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
- tiredness
- trouble with balance, coordination, and walking
- problems with thinking, such as forgetfulness or confusion, memory problems and hallucinations

- shortness of breath
- muscle weakness
- nausea

These are not all of 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.

- White opaque capsules, printing ink contains in addition FD & C blue #2 aluminum lake.
- Blue opaque capsules contain in addition magnesium stearate and FD & C blue #1. Printing ink contains in addition titanium dioxide.

Distributed by: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA; U.S. License No. 1713

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 06/2024

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STEVEN J LEMERY
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