▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION AUGTYRO® (REPOTRECTINIB) CAPSULES

1 NAME OF THE MEDICINE

repotrectinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

40 mg hard capsules

Each capsule contains 40 mg repotrectinib.

Excipient with known effect: Contains sulfites.

160 mg hard capsules

Each capsule contains 160 mg repotrectinib.

Excipient with known effect: Contains sulfites.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

40 mg hard capsules

Size#0, hard gelatin capsule with white opaque body and cap, and “REP 40” printed in blue ink on the cap.

160 mg hard capsules

Size #0. hard gelatin capsule with blue opaque body and cap, and “REP 160” printed in white ink on the cap.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with AUGTYRO should be initiated and supervised by physicians experienced in the use of anticancer medicinal products.

Before starting AUGTYRO, discontinue strong or moderate CYP3A4 inhibitors (see Section 4.5 *Interactions with other medicines and other forms of interaction)*, and check liver function (including bilirubin) and urate (see Section 4.4 *Special warnings and precautions for use*).

***ROS1* testing for patient selection**

A validated assay (such as one included in the Australian Register of Therapeutic Goods or one that has Australian accreditation) is required for the selection of patients with *ROS1*-positive locally advanced or metastatic NSCLC. *ROS1*-positive tumour status must be established prior to initiation of treatment with AUGTYRO.

Dosage and method of administration

The recommended dose is 160 mg orally once daily for 14 days, followed by 160 mg orally twice daily until disease progression or unacceptable toxicity.

Swallow capsules whole at the same time(s) each day. Do not open, crush, chew, or dissolve the contents of the capsule.

AUGTYRO may be taken with or without food.

Missed dose

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.

Dose modifications for adverse events

Recommended dose reductions for adverse reactions are provided in Table 1.

Table 1 Recommended dose reductions for adverse events (AE)

Dose	First dose reduction	Second dose reduction
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 for specific adverse reactions are provided in Table 2.

Table 2 Recommended dosage modifications for specific adverse events

Adverse events	Severity*	Dosage modification
Central nervous system effects	Intolerable Grade 2	• Withhold until less than or equal to Grade 1 or baseline. • Resume at same or reduced dose, as clinically appropriate.
	Grade 3	• Withhold until less than or equal to Grade 1 or baseline. • Resume at reduced dose.
	Grade 4	• Permanently discontinue.
Interstitial lung disease (ILD)/pneumonitis	Any Grade	• Withhold if ILD/pneumonitis is suspected. • Permanently discontinue if ILD/pneumonitis is confirmed.
Hepatotoxicity	Grade 3	• Withhold 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.

Adverse events	Severity*	Dosage modification
	ALT or AST greater than 3 times the upper limit of normal (ULN) with concurrent total bilirubin greater than 1.5 times ULN (in the absence of cholestasis or haemolysis)	• Permanently discontinue AUGTYRO
Creatine phosphokinase (CPK) elevation	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
Hyperuricaemia	Grade 3 or Grade 4	• Withhold until improvement of signs or symptoms. • Resume AUGTYRO at same or reduced dose
Other clinically relevant adverse reactions	Intolerable Grade 2	• Withhold until less than or equal to Grade 1 or baseline. • Resume at the same or reduced dose if resolution occurs within 4 weeks.
	Grade 3 or 4	• Withhold until adverse reaction resolves or improves to recovery or improvement to 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 4.0

DOSE IN SPECIAL POPULATIONS

Paediatric patients

The safety and efficacy of AUGTYRO in patients below 18 years of age with *ROS1*-positive NSCLC have not been established.

Elderly patients

No dose adjustment is required for elderly patients (≥ 65 years).

Patients with renal impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (eGFR-CKD-EPI 30 to 90 mL/min). The recommended dosage of repotrectinib has not been established in patients with severe renal impairment or kidney failure (eGFR-CKD-EPI <30 mL/min), and patients on dialysis (see Section 5.2 Pharmacokinetics).

Patients with hepatic impairment

No dose adjustment is recommended for patients with mild (total bilirubin > 1 to 1.5 times upper limit of normal [ULN] or AST > ULN) hepatic impairment. The recommended dosage of repotrectinib has not been established in patients with moderate (total bilirubin >1.5 to 3 times ULN with any AST) or severe (total bilirubin >3 times ULN with any AST) hepatic impairment (see Section 5.2 Pharmacokinetics).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Central nervous system (CNS)

AUGTYRO can cause a broad spectrum of CNS adverse reactions including dizziness, ataxia, and cognitive disorders (see 4.8 Adverse effects (undesirable effects)).

Advise patients and caregivers of these risks with AUGTYRO as they may influence the ability to drive and use machines. Advise patients not to drive or use machines if they are experiencing CNS adverse reactions. Withhold and then resume at the same or reduced dose upon improvement, or permanently discontinue AUGTYRO based on severity (see Section 4.2 Dose and method of administration).

Interstitial lung disease (ILD)/pneumonitis

AUGTYRO can cause ILD/pneumonitis. Advise patients to report its symptoms, which may include shortness of breath, cough, wheezing, chest pain or tightness, and haemoptysis. 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 Section 4.2 Dose and Method of Administration).

Hepatotoxicity

AUGTYRO can cause hepatotoxicity. 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 Section 4.2 Dose and Method of Administration).

Myalgia with creatinine phosphokinase (CPK) elevation

AUGTYRO can cause myalgia with or without creatine phosphokinase (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 Section 4.2 Dose and Method of Administration).

Hyperuricaemia

AUGTYRO can cause hyperuricaemia. 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 Section 4.2 Dose and Method of Administration).

Skeletal fractures

AUGTYRO increases the risk of skeletal fractures. 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.

Reproductive toxicity

Based on findings from animal studies, and its mechanism of action, AUGTYRO can cause fetal harm. Exposure during pregnancy should be avoided (see Section 4.6 Fertility, Pregnancy and Lactation).

Patients on a controlled sodium diet

AUGTYRO contains less than 1 mmol sodium (23 mg) per 40 mg and 160 mg capsule, this is to say essentially 'sodium free'.

Use in the elderly

No clinically meaningful differences in safety and efficacy between patients less than 65 years of age and patients 65 years of age or older.

Paediatric use

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

Effects on laboratory tests

See Table 4, in Section 4.8 Adverse effects (Undesirable effects).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

Interaction studies have only been performed in adults.

Effects of other drugs on AUGTYRO

Strong and Moderate CYP3A Inhibitors

Avoid concomitant use with strong or moderate CYP3A inhibitors. AUGTYRO should not be taken with foods that inhibit CYP3A4 such as grapefruit or grapefruit juice.

Concomitant use of AUGTYRO with a strong or a moderate CYP3A inhibitor may increase AUGTYRO exposure, which may increase the incidence and severity of adverse reactions of AUGTYRO. Discontinue CYP3A inhibitors for 3 to 5 elimination half-lives of the CYP3A inhibitor prior to initiating AUGTYRO.

P-gp Inhibitors

Avoid concomitant use with P-gp inhibitors. Concomitant use of AUGTYRO with a P-gp inhibitor may increase AUGTYRO exposure, which may increase the incidence and severity of adverse reactions of AUGTYRO.

Strong and Moderate CYP3A Inducers

Avoid concomitant use with strong or moderate CYP3A inducers. Concomitant use of AUGTYRO with a strong or moderate CYP3A inducer may decrease AUGTYRO plasma concentrations, which may decrease efficacy of AUGTYRO.

Effects of repotrectinib on other drugs

Certain CYP3A4 Substrates

Avoid concomitant use - unless otherwise recommended in its product 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 information.

AUGTYRO is a moderate CYP3A4 inducer. Concomitant use of AUGTYRO decreases the concentration of CYP3A4 substrates, which can reduce the efficacy of these substrates.

Contraceptives

AUGTYRO is a moderate CYP3A4 inducer, which can decrease progestin or oestrogen exposure to an extent that could reduce the effectiveness of hormonal contraceptives (see Section 4.6 Fertility, Pregnancy and Lactation).

Effects of repotrectinib on transporters and UGT

In vitro data indicate that repotrectinib may affect exposure to drugs that are of P-gp, BCRP or OATP1B1 substrates at clinically relevant concentrations. Based on *in vitro* data, interactions with UGT1A1, OATP1B3, MATE1 and MATE2-K are considered possible.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Studies to evaluate the effect repotrectinib on fertility have not been performed, so its effect on fertility (male and female) is unknown.

Contraception

Exposure during pregnancy to repotrectinib could cause fetal harm (see *Use in pregnancy*, below). Patients whose sperm could cause their partner to become pregnant should use condoms during treatment with AUGTYRO and for 4 months following the final dose.

Advise patients who could become pregnant to use effective non-hormonal contraception (since AUGTYRO can render some hormonal contraceptives ineffective) during treatment with AUGTYRO and for 2 months after the last dose.

Use in pregnancy (Category D)

There are no clinical data on repotrectinib use in pregnancy. Based on animal studies and its mechanism of action, repotrectinib may cause fetal harm when administered during pregnancy. Verify patient pregnancy status prior to initiating AUGTYRO therapy, and advise patients of the potential risk to a fetus.

Reproductive toxicology

In a preliminary embryo-fetal development study in rats, teratogenic effects (fetal external malformation of malrotated hindlimbs) post implantation loss and maternal effects (skin scabbing and abrasions in cervical and thoracic regions and increased body weight) were observed in pregnant rats from subclinical exposures (estimated approximate ER $_{AUC} \geq 0.2$ times the clinical exposure at the recommended dose based on AUC). Decreased fetal body weights were observed for females and for the combined sexes at 2.4-fold the human exposure based on estimated AUC.

There were no effects on male and female reproductive organs observed in general toxicology studies conducted in rats and monkeys at any dose level tested, which equated to exposures of up to approximately 2.4 times the human exposure at the 160 mg twice daily dose based on AUC.

Use in lactation

Repotrectinib has not been studied in patients who are breastfeeding. There are no data on the presence of repotrectinib in human milk or its effects on either the breastfed child or on milk production. Because of the potential adverse reactions in breastfed children from repotrectinib, patients should discontinue breastfeeding during treatment with AUGTYRO and for 10 days after the final dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

AUGTYRO has moderate influence on the ability to drive and use machines. Patients and caregivers should be advised of CNS effects with AUGTYRO as these effects may influence the ability to drive and use machines. Patients should be advised not to drive or operate hazardous machinery if they are experiencing CNS adverse effects (see Section 4.4 Special Warnings and Precautions for Use and Section 4.8 Adverse Effects).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety of AUGTYRO was assessed in 320 subjects with *ROS1*-positive NSCLC in the TRIDENT-1 study. 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. The median treatment duration of the recommended dose of AUGTYRO was 5.5 months.

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

Serious adverse events occurred in 33.1% of patients who received AUGTYRO. Serious adverse events in ≥2% of patients included pneumonia (3.4%), dyspnoea (3.4%), pleural effusion (3.4%), and hypoxia (3.1%). Fatal adverse events occurred in 4.1% of patients who received AUGTYRO, including pneumonia, pneumonia aspiration, cardiac arrest, sudden cardiac death, cardiac failure, hypoxia, dyspnoea, respiratory failure and disseminated intravascular coagulation.

Permanent discontinuation of AUGTYRO due to an adverse event occurred in 7.2% of patients. There were no specific adverse events that accounted for ≥1% of permanent discontinuations.

Dosage interruptions of AUGTYRO due to an adverse event occurred in 49.4% of patients. Adverse events that required dosage interruption in ≥2% of patients were dizziness, dyspnoea, muscular weakness, ataxia, pneumonia, anaemia, hypoxia, COVID-19, blood creatinine phosphokinase increased, and alanine aminotransferase increased.

Dose reductions of AUGTYRO due to an adverse event occurred in 35% of patients. Adverse events that required dosage reductions in ≥2% of patients included dizziness, ataxia, muscular weakness, dyspnoea and blood creatinine phosphokinase increased.

Table 3 and Table 4 summarises adverse events in *ROS1*-positive NSCLC patients treated at a dose of 160 mg orally once daily for the first 14 days then increased to 160 mg orally twice daily in TRIDENT-1 study.

Table 3: Adverse Events (≥10%) in Patients with *ROS1*-positive NSCLC Who Received the Recommended Dose of AUGTYRO in TRIDENT-1.

Adverse Event	AUGTYRO N = 320	
	All Grades (%)	Grade ≥3 (%)
Nervous System Disorder		
Dizziness[a]	64.4	1.9
Dysgeusia[b]	51.6	0
Peripheral neuropathy[c]	50.0	1.6
Ataxia[d]	27.8	0.6
Cognitive impairment[e]	23.8	0.9
Headache[f]	18.8	0
Gastrointestinal Disorders		
Constipation	36.6	0
Nausea	18.1	0.6
Diarrhoea	12.5	0.3
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnoea[g]	29.7	6.6
Cough[h]	17.2	0
General Disorders		
Fatigue[i]	25.6	0.9
Oedema[j]	15.3	0.6

Adverse Event	AUGTYRO N = 320	
Musculoskeletal and Connective Tissue Disorders		
Muscular weakness	21.9	2.2
Myalgia[k]	11.6	0.6
Metabolism and Nutritional		
Increased weight	15.6	3.1
Eye Disorders		
Vision disorders[l]	10.9	0.3

[l] 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, dysaesthesia, 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 dyspnoea and dyspnoea exertional

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

[i] Includes terms fatigue and asthenia

[j] Includes terms generalised oedema, periorbital oedema, localised oedema, face oedema, oedema peripheral, oedema, eye oedema, scrotal oedema

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

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

Clinically relevant adverse events occurring in <10% of ROS1 NSCLC patients receiving AUGTYRO were pneumonia (8.1%), vomiting (9.7%), decreased appetite (8.4%), pyrexia (7.8%) and fall (2.8%).

Description of selected adverse events

Central nervous system (CNS) reactions

Among the 320 patients who received AUGTYRO in Study TRIDENT-1, a broad spectrum of central nervous system (CNS) adverse events including dizziness, ataxia, and cognitive disorders occurred in 77% of patients, with Grade 3 or 4 events occurring in 3.8% of patients.

Dizziness, including vertigo, occurred in 61.6% of patients; Grade 3 dizziness occurred in 1.6% of patients. The median time to onset was 7 days (1 day to 1.4 years). Dose interruption was required in 6.9% of patients, and 9.4% required dose reduction of AUGTYRO due to dizziness.

Ataxia, including gait disturbance and balance disorder, occurred in 28.0% of patients; Grade 3 ataxia occurred in 0.6% of patients. The median time to onset was 18 days (1 day to 589 days). Dose interruption was required in 5% of patients, 7% required dose reduction, and one patient (0.3%) permanently discontinued AUGTYRO due to ataxia.

Cognitive disorders, including memory impairment and disturbance in attention, occurred in 24% of patients. Cognitive impairment included memory impairment (14%), disturbance in attention (11%), and confusional state (1.6%); Grade 3 cognitive disorders occurred in 0.9% of patients. The median time to onset of cognitive disorders was 38 days (1 day to 519 days). Dose interruption was required in 1.9% of patients, 2.2% required dose reduction, and 0.3% patients permanently discontinued AUGTYRO due to cognitive adverse events.

Mood disorders occurred in 6% of patients. Mood disorders occurring in >1% of patients included anxiety (3.1%); Grade 4 mood disorders (mania) occurred in 0.3% of patients. Dose interruption was required in 0.3% of patients and 0.2% of patients required a dose reduction due to mood disorders.

Sleep disorders including insomnia and hypersomnia occurred in 17% of patients. Sleep disorders observed in > 1% of patients were somnolence (8%), insomnia (6%) and hypersomnia (1.6%). Dose interruption was required in 0% of patients, and 0% 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.

Interstitial lung disease (ILD)/pneumonitis

Among the 320 patients treated with AUGTYRO, ILD/pneumonitis (pneumonitis [2.8%] and ILD [0%]) occurred in 2.8% of patients; Grade 3 ILD/pneumonitis occurred in 1.3% of patients. The median time to onset was 42 days (19 days to 356 days). Dose interruption was required in 1.9% of patients, 0.5% of patients required dose reduction, and 0.6% of patients permanently discontinued AUGTYRO due to ILD/pneumonitis.

Hepatotoxicity

Among the 320 patients treated with AUGTYRO, increased alanine transaminase (ALT) occurred in 25%, increased aspartate aminotransferase (AST) occurred in 22%, including Grade 3 or 4 increased ALT in 1.6% and increased AST in 1.6%. The median time to onset of increased ALT or AST was 15 days (range: 1 day to 729 days). Increased ALT or AST leading to dose interruptions or reductions occurred in 2.2% and 0.6% of patients, respectively.

Myalgia with creatinine phosphokinase (CPK) elevation

Among the 320 patients treated with AUGTYRO, myalgia occurred in 12% of patients, with Grade 3 in 0.6%. Median time to onset of myalgia was 40 days (range: 3 days to 731 days). Concurrent increased CPK within a 7-day window was observed in 3.7% of patients. AUGTYRO was interrupted in 1.3% of patients with myalgia.

Hyperuricaemia

Among the 320 patients treated with AUGTYRO, 21 patients (4.1%) experienced hyperuricaemia reported as an adverse reaction and 0.3% of patients experienced Grade 3 or 4 hyperuricaemia. One patient without pre-existing gout required urate-lowering medication.

Skeletal fractures

Among 320 adult patients who received AUGTYRO, fractures occurred in 2.5%. Fractures involved the ribs (0.6%), feet (0.3%), spine (0.3%), acetabulum (0.3%), sternum (0.3%), ankles (0.3%) and upper limb (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 496 days). AUGTYRO was interrupted in 0.6% of patients.

Table 4 Laboratory Abnormalities (≥20%) Worsening from Baseline in ROS1-positive NSCLC Patients who received the recommended dose of AUGTYRO in TRIDENT-1.

Laboratory Abnormality	AUGTYRO (N=320) NCI CTCAE Grade[a]	
	All Grade (%)	Grade 3 or 4 (%)
Haematology		
Low Haemoglobin	76.8	7.0
Low Lymphocytes	42.3	10.6
Low Leukocytes	38.9	4.1
Low Neutrophils	33.8	8.4

Coagulation		
High Activated Partial Thromboplastin Time	26.7	0.3
High Prothrombin Intl. Normalised Ratio	23.3	0
Chemistry		
High Creatine Kinase	61.4	6.6
High Gamma Glutamyl Transferase	50.0	12.9
High Aspartate Aminotransferase	40.2	2.2
High Alanine Aminotransferase	36.8	3.1
High Sodium	34.5	0.3
High cholesterol	30.0	0
High Alkaline Phosphatase	25.2	1.9
High Glucose	24.2	1.9
High Urate	22.7	12.6
High Potassium	22.3	0.3
Low Glomerular Filtration Rate	24.8	2.0
Low Phosphate	20.3	6.0
Low Glucose	21.1	0.3

[a.]Based on NCI CTCAE v4.03

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Patients who experience overdose should be closely supervised and supportive care instituted.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Repotrectinib is a tyrosine kinase inhibitor (TKI) that inhibits the proto-oncogene tyrosine-protein kinase ROS1 (ROS1).

Fusion proteins containing a ROS1 kinase domain can drive oncogenesis via constitutive activation of downstream signalling pathways and unconstrained cell proliferation. Point mutations within the ROS1 kinase domain, including those affecting the solvent front (e.g. G2032R) or gatekeeper residue (e.g. L2026M), can confer resistance to treatment with TKIs through steric hindrance of drug binding. Repotrectinib is a compact, macrocyclic TKI that binds entirely within the ATP-binding pocket of the kinase domain and lacks structural extensions into the solvent front region.

In a biochemical kinase assay, repotrectinib inhibited wild-type ROS1 and ROS1^{G2032R} with IC_{50} values of 0.07 and 0.46 nM, respectively. In cell-based assays using Ba/F3 cells engineered to express ROS1 fusion proteins (CD74-ROS1 or SDC4-ROS1) or corresponding mutant variants (CD74-ROS1^{G2032R}, CD74-ROS1^{D2033N}, CD74-ROS1^{L2026M}, and SDC4-ROS1^{G2032R}), repotrectinib inhibited cell proliferation with IC_{50} values ranging from <0.2 to 10 nM.

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.

Clinical trials

The efficacy of AUGTYRO was evaluated in adult patients with *ROS1*-positive locally advanced or metastatic NSCLC in a phase 1/2, multicentre, single-arm, open-label, multi-cohort clinical study (TRIDENT-1). Phase 1 comprised dose escalation, and in phase 2 patients received repotrectinib at the recommended dose (160 mg orally once daily for the first 14 days of treatment, followed by 160 mg orally twice daily until disease progression or unacceptable toxicity). Patients required ECOG performance status ≤1 and measurable disease per RECIST v 1.1. All patients were assessed for CNS lesions at baseline, and patients with symptomatic brain metastases were excluded from the trial.

Two efficacy cohorts were defined based on prior receipt of treatment with a tyrosine kinase inhibitor of ROS1 (ROS1 TKI):

- TKI naïve
  Patients who had not received any prior treatment with a ROS1 TKI, but had received up to 1 prior line of platinum-based chemotherapy and/or immunotherapy (n=71, including 8 phase 1 and 63 phase 2 participants)
- TKI pretreated
  56 patients who had received 1 prior ROS1 TKI but no prior platinum-based chemotherapy or immunotherapy (n=56, including 3 phase 1 and 53 phase 2 participants)

Identification of *ROS1* gene fusions in tumour specimens was prospectively determined in local laboratories using next-generation sequencing (NGS), polymerase chain reaction (PCR) or fluorescence in situ hybridisation (FISH) tests. All *ROS1*-positive tumours by local FISH testing required central laboratory confirmation using an analytically validated NGS test. *ROS1* gene fusions were identified by NGS (51%), FISH (26%) or PCR (23%).

Key efficacy endpoints were overall response rate (ORR) and duration of response (DOR) assessed by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. Intracranial response according to modified RECIST v1.1 was also assessed by BICR. Tumour assessments with imaging were performed at least every 8 weeks.

Among the 71 ROS1 inhibitor naïve patients, the median age was 57 years (range: 28 – 80), 26.8% and 5.6% were 65 years or older and 75 years or older respectively. The majority were female (61%) Asian (68%) or White (25%); and had never smoked (63%). Baseline ECOG performance status was 0 (34%) and 1 (66%). At baseline, 94% of patients had metastatic disease, 24% of patients had CNS metastases by BICR; 97% of patients had adenocarcinoma; 28% of patients had prior platinum-based chemotherapy for locally advanced or metastatic disease.

Among the 56 patients who had received 1 prior ROS1 TKI (crizotinib 82%, entrectinib 16%, and ceritinib 2%) with no prior platinum-based chemotherapy, the median age was 57 years, (range: 33-78): 28% were 65 years or older and 9% were 75 years or older. The majority were female (68%), Asian (48%) or White (45%); never smoked (64%); and ECOG performance status of 1 at baseline (68%). At baseline, 98% patients had metastatic disease, 46% had CNS metastases by BICR, and 95% had adenocarcinoma.

Efficacy results for patients with a minimum follow up of 14.2 months (data cut-off date 19 DEC 2022) are summarised in Table 5.

Table 5: Efficacy results in *ROS1*-positive NSCLC patients per BICR assessment

Efficacy parameters	**TKI naïve (N = 71)**	**TKI pretreated[a] (N = 56)**
Confirmed objective response rate, % (95% CI)	79 (68, 88)	38 (25, 52)
Complete responses, N (%)	7 (10)	3 (5)

Partial responses, N (%)	49 (69)	18 (32)
Median duration of response (DOR), months (95% CI)	34.1 (25.6, NE)	14.8 (7.6, NE)
Range (months)	1.4+ – 42.4+	3.6 – 22.9+
% with DOR at least 6 months (95% CI)	90.8 (83, 99)	75.9 (58, 94)
% with DOR at least 9 months (95% CI)	88.9 (81, 97)	60.7 (39, 82)
% with DOR at least 12 months (95% CI)	83.1 (73, 93)	55.7 (34, 77)

Abbreviations: CI = confidence interval; NE = not evaluable; "+" indicates ongoing response
DOR are by Kaplan-Meier estimates.
[a] Patients who had received one prior TKI and no chemotherapy

The median time to response was 1.84 (range 0.9, 5.6) months for the TKI naïve cohort and 1.81 (range 1.6, 3.6) months for the TKI pretreated cohort.

Among 9 patients in the TKI naïve cohort who had measurable CNS metastases at baseline as assessed by BICR, intracranial response was observed in 8 patients (1 CR and 7 PR). Among 13 patients in the TKI pretreated cohort who had measurable CNS metastases at baseline as assessed by BICR, intracranial response was observed in 5 patients (5 PR).

Among the TKI pretreated cohort, mutations associated with TKI resistance were detected in tumour samples for 100 patients following their prior TKI therapy. Amongst 17 patients with a solvent front mutation (G2032R) at TRIDENT-1 study entry, an objective response was observed in 10 patients. Responses following repotrectinib treatment were also observed in patients with gatekeeper ($ROS1^{L2026M}$), and other mutations ($ROS1^{S1986F/Y}$).

5.2 PHARMACOKINETIC PROPERTIES

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 ($AUC_{0\text{-}24h,ss}$) is 7210 (40.1%) ng•h/mL following the approved recommended twice daily dosage in patients with cancer. Repotrectinib C_{max} and $AUC_{0\text{-}inf}$ increases are 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 of repotrectinib.

Absorption

The geometric mean (CV%) absolute bioavailability of repotrectinib is 45.7% (19.6%). Peak repotrectinib concentration occurred at approximately 2-3 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 repoterctinib. Binding of repotrectinib to human plasma protein was 95.4% *in vitro*. Repotrectinib binding to plasma protein was 95.4% *in vitro*. The blood-to-plasma ratio was 0.56 *in vitro.*

Metabolism

Repotrectinib is primarily metabolised by CYP3A4 followed by secondary glucuronidation.

Elimination

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

The repotrectinib mean terminal half-life is approximately 60.7 hours for patients with cancer following a single dose. The steady state repotrectinib terminal half-life is approximately 40.3 hours 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 repotrectinib.

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 faeces.

Pharmacokinetics in special populations

Renal impairment

The effect of renal impairment on the pharmacokinetics of repotrectinib was evaluated by a population PK analysis in patients. No clinically significant differences in the pharmacokinetics of repotrectinib were found between patients with mild or moderate (eGFR-CKD-EPI 30 to 90 mL/min) renal impairment and patients with normal renal function. Repotrectinib has not been studied in patients with severe renal impairment (eGFR-CKD-EPI <30 mL/min) including those with end-stage renal failure on dialysis.

Hepatic impairment

The effect of hepatic impairment on the pharmacokinetics of repotrectinib was evaluated by population PK analysis in patients. No clinically significant differences in the pharmacokinetics of repotrectinib were found between patients with mild hepatic impairment (total bilirubin >1.0 to 1.5 times ULN or AST > ULN) and patients with normal hepatic function. The pharmacokinetics of repotrectinib have not been established in patients with moderate (total bilirubin >1.5 to 3 x ULN with any AST) or severe (total bilirubin >3 x ULN with any AST) hepatic impairment.

Effects of age, body weight, race and gender

No clinically significant differences in the pharmacokinetics of repotrectinib were identified based on gender, age (12 years to 93 years), body weight (39.5 kg to 169 kg), race (Caucasian, Asian, and Black or African American).

Effect of CYP3A and P-gp inhibitors on repotrectinib

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

Effect of CYP3A and P-gp inducers on repotrectinib

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

Effect of repotrectinib on CYP3A substrates

Midazolam (CYP3A substrate $AUC_{0\text{-}inf}$ decreased by 69% and C_{max} by 48% following concomitant use in subjects that 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 (gastrointestinal tract).

*Other Metabolic Pathway*s: Repotrectinib inhibits UGT1A1.

Transporter Systems: Repotrectinib inhibits P-gp, BCRP, OATP1B1, MATE1 and MATE2-K. Repotrectinib is a substrate for P-gp.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Repotrectinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay. Repotrectinib was aneugenic in an *in vitro* assay in human lymphoblastoid TK6 cells and positive for micronuclei formation *in vivo* in the bone marrow of rats at a threshold of >100 mg/kg nominal dose (resulting in exposures approximately 4 times the human exposure at the 160 mg twice daily dose based on C_{max}).

Carcinogenicity

Studies to evaluate the carcinogenic potential of repotrectinib have not been performed.

Repeat dose toxicity studies

Following repeat-dose oral administration of repotrectinib daily for up to 3 months in Sprague Dawley rats and cynomolgus monkeys, the main toxicities observed were skin scabs/ulcerations at ≥ 0.33 times the human exposures based on AUC; severe CNS effects (i.e. ataxia, tremors) in rats at ~ 2.1 times the human exposures based on AUC; and gastrointestinal tract effects (i.e. emesis, watery faeces, and minimal subacute/chronic inflammation and/or minimal to mild mucosal gland hyperplasia in the large intestines) in monkeys at ≥ 0.11 times the human exposures based on AUC in monkeys. The skin ulcerations were considered secondary to TRK inhibition resulting in loss of sensation and bodily injury.

Juvenile rat toxicity studies

The effects of repotrectinib in juvenile rats were investigated in dose range finding (postnatal day [PND] 12 to PND 40) and definitive (PND 12 to PND 70) repeat-dose juvenile toxicity studies. CNS-related mortality was observed in very young rats (PND 13 to PND 15; approximately equivalent to infant) at ≥ 1.5 times the adolescent human exposure based on AUC. Decreased effects on growth (decreased body weight, food consumption and femur length) were observed at ≥ 0.035 times the adolescent human exposure based on AUC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule content

Microcrystalline cellulose

Sodium lauryl sulfate

Croscarmellose sodium

Silicon dioxide

Magnesium stearate (for 160 mg hard capsule only)

Capsule shell content

Gelatin

Titanium dioxide

Brilliant blue FCF (for 160 mg hard capsule only)

Printing ink (40mg hard capsule)

TekPrint™ SB-6018 Blue Ink

Printing ink (160mg hard capsule)

TekPrint SW-0012 White Ink

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

AUGTYRO 40 mg hard capsules

120-cc and 200-cc, high-density polyethylene (HDPE) bottles with 2-piece child-resistant continuous thread (CRCT) polypropylene (PP) closures.

Pack sizes: 60 and 120 hard capsules

AUGTYRO 160 mg hard capsules

Polyvinyl chloride/Aclar (PVC/Aclar) clear blister with push through aluminium foil lidding. Aclar refers to polychlorotrifluoroethylene (PCTFE).

Pack sizes: 20 and 60 hard capsules.

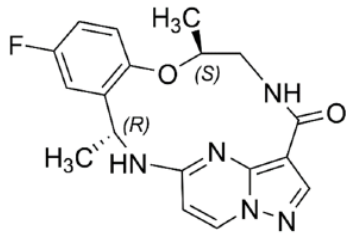
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicinal product or waste material should be discarded in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

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 g/mol. 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.

CAS number

Repotrectinib: CAS: 1802220-02-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine.

8 SPONSOR

Bristol-Myers Squibb Australia Pty Ltd

4 Nexus Court, Mulgrave,
Victoria 3170, Australia.
Toll free number: 1800 067 567
Email: MedInfo.Australia@bms.com

9 DATE OF FIRST APPROVAL (ARTG ENTRY)

25 July 2025

10 DATE OF REVISION OF THE TEXT

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
V1.0	This is the first version of the PI.

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