ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

AUGTYRO 40 mg hard capsules
AUGTYRO 160 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AUGTYRO 40 mg hard capsules

Each hard capsule contains 40 mg repotrectinib.

AUGTYRO 160 mg hard capsules

Each hard capsule contains 160 mg repotrectinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard (capsule)

AUGTYRO 40 mg hard capsules

Size 0 (21.7 mm in length), hard gelatin capsule with white opaque body and cap, and “REP 40” printed in blue ink on the cap.

AUGTYRO 160 mg hard capsules

Size 0 (21.7 mm in length), 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 advanced non-small cell lung cancer (NSCLC).

AUGTYRO as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older with advanced solid tumours expressing a *NTRK* gene fusion, and

- who have received a prior NTRK inhibitor, or
- have not received a prior NTRK inhibitor and treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted (see sections 4.4 and 5.1)

4.2 Posology and method of administration

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

ROS1 testing
Patient selection for treatment with repotrectinib, based on *ROS1*-positive status in NSCLC should be assessed by a CE-marked IVD with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used (see sections 4.1, and 5.1).

NTRK testing
Patient selection for treatment with repotrectinib, based on *NTRK*-positive status in solid tumours should be assessed by a CE-marked IVD with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used (see sections 4.1, 4.4 and 5.1).

Posology

ROS1-positive non-small cell lung cancer
The recommended dose in adults is 160 mg repotrectinib once daily for 14 days, followed by 160 mg repotrectinib twice daily until disease progression or unacceptable toxicity.

NTRK gene fusion-positive solid tumours
The recommended dose in adults and paediatric patients 12 year and older is 160 mg repotrectinib once daily for 14 days, followed by 160 mg repotrectinib twice daily until disease progression or unacceptable toxicity.

Missed dose
If a dose is missed or if a patient vomits at any time after taking a dose, subsequent doses should be resumed as prescribed. Two doses should not be taken at the same time.

Dose modifications for adverse reactions
The recommended dose reductions for adverse reactions are provided in Table 1:

Table 1: Recommended dose reductions for adverse reactions

Prescribed dose	**Dose reduction**	
	First occurrence	**Second occurrence**
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 dose modifications for specific adverse reactions are provided in Table 2 (see sections 4.4 and 4.8).

Table 2: Recommended dose modifications for specific adverse reactions

Adverse reactions	**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.

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 NCI Common Terminology Criteria for Adverse Events 4.0

Special populations

Elderly
No dose adjustment is required for elderly patients (≥ 65 years) (see section 5.2).

Renal impairment
No dose adjustment is required for patients with mild or moderate renal impairment. AUGTYRO has not been studied in patients with severe renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is required for patients with mild hepatic impairment (total bilirubin > 1.0 to 1.5 times ULN or AST > ULN) AUGTYRO has not been studied in patients with moderate (total bilirubin > 1.5 to 3 times ULN) or severe (total bilirubin > 3 times ULN) hepatic impairment, and AUGTYRO should not be used in patients with moderate/severe hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

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

The safety and efficacy of AUGTYRO in paediatric patients below 12 years of age with *NTRK*-positive solid tumours have not been established. Currently, available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made.

Method of administration

AUGTYRO is for oral use. The capsules should be swallowed whole at the same time every day. The capsules must not be opened, crushed, chewed, and the contents of the capsule must not be dissolved.

AUGTYRO may be taken with or without food (see section 5.2) but should not be taken with grapefruit, grapefruit juice or Seville oranges (see section 4.5).

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

Efficacy across tumour types

The benefit of AUGTYRO has been established in single-arm studies encompassing adult patients (N = 88) whose tumours exhibit *NTRK* gene fusions. Favourable effects of AUGTYRO have been shown based on overall response rate and response duration in a limited number of tumour types. The effect may be quantitatively different depending on tumour type, as well as on concomitant genomic alterations (see section 5.1).

Central nervous system (CNS)

A broad spectrum of CNS adverse reactions has been reported in patients receiving AUGTYRO including dizziness, ataxia, and cognitive disorders (see section 4.8).

Patients should be advised of these risks with AUGTYRO as they may influence the ability to drive and use machines. Patients should be advised not to drive or use machines if they are experiencing CNS adverse reactions (see section 4.7). AUGTYRO should be withheld and then resumed at the same or reduced dose upon improvement, or permanently discontinued based on severity (see section 4.2).

Interstitial lung disease (ILD)/Pneumonitis

Patients should be advised to report symptoms of ILD/pneumonitis, which may include shortness of breath, cough, wheezing, chest pain or tightness, and haemoptysis. Patients should be monitored for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. AUGTYRO should be withheld in patients with suspected ILD/pneumonitis and permanently discontinued if ILD/pneumonitis is confirmed (see section 4.2).

Skeletal fractures

Skeletal fractures have been reported in adults and paediatric patients treated with AUGTYRO across clinical studies. In adult and paediatric patients, some fractures occurred in the setting of a fall or other trauma to the affected area. Radiologic abnormalities possibly indicative of tumour involvement were reported in some patients. In both adult and paediatric patients, most fractures were lower extremity fractures (e.g., fibula, tibia, or foot). Patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures should be promptly evaluated.

Hepatotoxicity

Drug-induced hepatotoxicity has been reported in patients treated with AUGTYRO (see section 4.8). Liver function tests including ALT, AST and bilirubin should be monitored as clinically indicated.

Hepatic impairment

AUGTYRO has not been studied in patients with moderate or severe hepatic impairment. AUGTYRO should not be used in patients with moderate or severe hepatic impairment due to potential risk of over-exposure and increased risk of adverse events (see sections 4.2 and 5.2).

Contraception in female and male

AUGTYRO may cause foetal harm when administered to a pregnant woman (see section 5.3).

Women of childbearing potential should have medically supervised pregnancy testing prior to initiating AUGTYRO therapy. Women of childbearing potential must use highly effective contraception during treatment with AUGTYRO and for 2 months following the final dose. AUGTYRO may reduce the effectiveness of systemically acting hormonal contraceptives including oral contraceptives (see sections 4.5 and 4.6).

Male patients with female partners of childbearing potential must use condoms during treatment with AUGTYRO and for 4 months after the final dose (see sections 4.6 and 5.3).

Paediatric population

Long-term safety data are unavailable on the use of AUGTYRO in paediatric patients 12 years of age and older.

Drug interactions

Co-administration of AUGTYRO use with a strong or moderate CYP3A/P-gp inhibitor increases repotrectinib plasma concentrations (see section 4.5), which may increase the risk of adverse reactions. Co-administration of AUGTYRO with a strong or moderate CYP3A/P-gp inhibitor should be avoided.

During treatment with AUGTYRO, the consumption of grapefruit and grapefruit products should be avoided.

Co-administration of AUGTYRO with a strong or moderate CYP3A/P-gp inducer decreases repotrectinib concentrations (see section 4.5), which may reduce efficacy of AUGTYRO, and should be avoided.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Based on *in vitro* data repotrectinib is a substrate for CYP3A4 and P-gp.

Effects of other agents on repotrectinib

Effect of CYP3A4 inhibitors and P-gp inhibitors on repotrectinib
Co-administration of multiple oral doses of itraconazole (a strong CYP3A4 and P-gp inhibitor) with a single 80 mg dose of repotrectinib increased repotrectinib $AUC_{0\text{-}inf}$ by 5.9-fold and C_{max} by 1.7-fold. Co-administration of AUGTYRO with strong or moderate CYP3A4 or P-gp inhibitors (including but not limited to ritonavir, saquinavir, ketoconazole, itraconazole, voriconazole, posaconazole, verapamil, nifedipine, felodipine, fluvoxamine, grapefruit, or Seville oranges) increases repotrectinib plasma concentrations and should thus be avoided (see section 4.4).

Effect of CYP3A4 and P-gp inducers on repotrectinib
Co-administration of multiple oral doses of rifampicin (a strong CYP3A4 and P-gp inducer) with a single 160 mg repotrectinib dose reduced repotrectinib $AUC_{0\text{-}inf}$ by 92% and C_{max} by 79%. Co-administration of AUGTYRO with strong or moderate CYP3A4 or P-gp inducers (including but not limited to carbamazepine, phenytoin, rifampicin, St. John's Wort- *Hypericum perforatum*, apalutamide, ritonavir) decreases repotrectinib plasma concentrations and should thus be avoided (see section 4.4).

Effects of repotrectinib on other agents

Effect of repotrectinib on CYP3A4 substrates
Repotrectinib is a moderate CYP3A4 inducer. Co-administration of 160 mg repotrectinib once daily for 14 days followed by twice daily dosing for 7 days reduced $AUC_{0\text{-}inf}$ by 69% and C_{max} by 48% of a single oral dose of midazolam (a CYP3A4 substrate). Caution is advised when CYP3A4 substrates (including but not limited to cisapride, cyclosporin, fentanyl, tacrolimus, alfentanil, sirolimus,

everolimus, lovastatin, and simvastatin) are co-administered with repotrectinib, due to risk of therapeutic failure.

Effect of repotrectinib on CYP2B6 substrates
In vitro studies indicate that repotrectinib is a CYP2B6 inducer. Co-administration of AUGTYRO with sensitive substrates of CYP2B6 substrates (including but not limited to bupropion, efavirenz) may decrease their exposure.

Effect of repotrectinib on substrates of PXR regulated enzymes
In vitro studies indicate that repotrectinib may induce pregnane X receptor (PXR) regulated enzymes that include CYP2C8, CYP2C9, CYP2C19 and UGT. *In vitro* data also indicate that repotrectinib inhibits CYP2C8, CYP2C9 and UGT1A1. The *in vivo* net effect of induction and inhibition, or its clinical relevance, is not known. Co-administration of AUGTYRO with CYP2C8, CYP2C9 or CYP2C19 substrates (including but not limited to repaglinide, warfarin, tolbutamide or omeprazole) may alter their exposure.

Effect of repotrectinib on other transporter substrates
In vitro data indicate that repotrectinib inhibits P-gp, breast cancer resistant protein (BCRP), organic anion-transporting polypeptide (OATP1B1), multidrug and toxin extrusion protein (MATE1) and MATE2-K. Co-administration of AUGTYRO with sensitive substrates of P-gp (including but not limited to dabigatran etexilate, digoxin, edoxaban, or fexofenadine), BCRP (including but not limited to methotrexate, rosuvastatin, sulfasalazine), OATP1B1 (including but not limited to valsartan, statins), MATE1 or MATE2-K (including but not limited to metformin) may increase their exposure. The clinical relevance is unknown.

Oral contraceptives
Repotrectinib is a moderate CYP3A4 inducer, which can decrease progestin or oestrogen exposure to an extent that could reduce the effectiveness of systemically acting hormonal contraceptives including oral contraceptives. Thus, women using systemically acting hormonal contraceptives are advised to use a barrier method (see section 4.6).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

Female patients of childbearing potential should have medically supervised pregnancy testing prior to initiating AUGTYRO therapy.

Female patients of childbearing potential must use highly effective contraception during treatment with AUGTYRO and for at least 2 months following the final dose. AUGTYRO may reduce the effectiveness of systemically acting hormonal contraceptives including oral contraceptives. If hormonal contraception is used, females of childbearing potential should be advised to use an additional barrier method of contraception (see section 4.5).

Male patients with female partners of childbearing potential must use condoms during treatment and for 4 months following the final dose of AUGTYRO.

Pregnancy

There are no available data on AUGTYRO use in pregnant women. Based on animal studies and its mechanism of action, repotrectinib may cause foetal harm when administered to pregnant women. AUGTYRO should not be used unless clinical condition of the woman requires treatment with

AUGTYRO. Women of childbearing potential have to use highly effective contraception (see sections 4.4 and 5.3).

Breast-feeding

It is unknown whether repotrectinib or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with AUGTYRO and for 10 days after the final dose.

Fertility

No fertility studies have been conducted with repotrectinib (see section 5.3). The effect of repotrectinib on male and female fertility is unknown.

4.7 Effects on ability to drive and use machines

AUGTYRO has moderate influence on the ability to drive and use machines. Patients should be advised of potential CNS effects and vision disorders with AUGTYRO as these effects may influence the ability to drive and use machines. Patients should be advised not to drive or use machines if they are experiencing CNS adverse reactions and vision disorders (see sections 4.4 and 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions in adults were dizziness (65%), dysgeusia (57%), constipation (39%), paraesthesia (39%), anaemia (38%), and dyspnoea (31%). The most common serious adverse reactions were pneumonia (6.2%), dyspnoea (3.5%), pleural effusion (3.0%), pyrexia (1.2%), muscular weakness (1.1%), anaemia (1.1%), and pneumonitis (1.1%). Grade ≥ 3 adverse reactions occurred in 43% of patients and anaemia (8.8%), dyspnoea (6.7%), pneumonia (5.7%), blood creatine phosphokinase increased (3.4%), weight increased (3.2%), aspartate aminotransferase increased (2.7%), pleural effusion (2.3%), and neutrophil count decreased (2.1%) were the most frequently reported. Permanent discontinuation due to an adverse reaction occurred in 6.2% patients.

Tabulated list of adverse reactions

Tables 3 and 4 summarise the adverse reactions reported in patients treated with AUGTYRO in the TRIDENT-1 study in adults (n = 565) and in the CARE study (n = 38) including paediatric patients respectively. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Unless otherwise stated, the frequencies of adverse reactions are based on all-cause adverse event frequencies identified in patients exposed to AUGTYRO with a median duration of 7.6 months in clinical study. See section 5.1 for information on the main clinical study.

Table 3: Adverse reactions occurring in adult patients treated with AUGTYRO

		% All Grades	**% ≥ 3 Grades**
Infections and infestations			
Very common	pneumonia	10.3	5.7
Blood and lymphatic system disorders			
Very common	anaemia	38.1	8.8

		% All Grades	% ≥ 3 Grades
Metabolism and nutrition disorders			
Common	hyperuricaemia[a]	5.0	0.7
Nervous system disorders			
Very common	dizziness[b]	65.5	3.2
	ataxia[c]	29.0	0.5
	cognitive disorders[d]	22.3	1.2
	paraesthesia[e],	39.1	0.7
	peripheral sensory neuropathy[f]	20.2	1.1
	sleep disorders[g]	17.3	0.2
	headache	20.0	0.4
	dysgeusia[h]	56.5	0
Eye disorders			
Very common	vision disorders[i]	14.2	0.5
Respiratory, thoracic and mediastinal disorders			
Very common	dyspnoea	31.3	6.7
	cough	18.9	0.2
Common	pneumonitis[j]	3.2	0.9
	pleural effusion	7.1	2.3
Gastrointestinal disorders			
Very common	nausea	20.7	1.2
	vomiting	14.5	1.1
	constipation	39.3	0.2
	diarrhoea	15.0	0.9
Common	abdominal pain	7.3	0.5
Musculoskeletal and connective tissue disorders			
Very common	muscular weakness	21.6	1.9
	pain in extremity	11.9	0.4
	arthralgia	15.2	0.4
	myalgia	12.2	0.5
	back pain	10.1	0.5
Common	skeletal fractures[k]	3.5	0.5
General disorders and administration site conditions			
Very common	pyrexia	12.7	0.7
	fatigue	24.8	1.2
	decreased appetite	11.3	0.4
	oedema peripheral	11.7	0
Investigations			
Very common	blood creatine phosphokinase increased	17.5	3.4
	weight increased	14.7	3.2
	alanine aminotransferase increased	22.1	1.9
	aspartate aminotransferase increased	20.9	2.7

		% All Grades	% ≥ 3 Grades
Common	lymphocyte count decreased	4.6	1.6
	white blood cell count decreased	9.0	0.9
	neutrophil count decreased	8.0	2.1
	gamma-glutamyltransferase increased	6.7	1.2
	blood alkaline phosphatase increased	8.3	1.1
Injury, poisoning and procedural complications			
Common	fall	4.6	0.5

[a] Hyperuricaemia (hyperuricaemia, increased blood uric acid)
[b]Dizziness (dizziness, vertigo, dizziness postural, dizziness exertional, vertigo positional)
[c] Ataxia (ataxia, gait disturbance, balance disorder, cerebellar ataxia, coordination abnormal, nystagmus)
[d] Cognitive disorders (memory impairment, disturbance in attention, cognitive disorder, confusional state, delirium, amnesia, attention deficit hyperactivity disorder, aphasia, altered state of consciousness, depressed level of consciousness, bradyphrenia, delusion, dysgraphia, hallucination, intellectual disability, mental disorder, mental status changes, neurological decompensation)
[e] Paraesthesia (paraesthesia, hypoaesthesia, dysaesthesia, burning sensation, anaesthesia, formication)
[f] Peripheral sensory neuropathy (neuralgia, neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, polyneuropathy)
[g] Sleep disorders (somnolence, insomnia, hypersomnia, sleep apnoea syndrome, sleep disorder, abnormal dreams, narcolepsy, obstructive sleep apnoea syndrome, snoring)
[h] Dysgeusia (dysgeusia, taste disorder, ageusia, sensory disturbance, allodynia, hypogeusia, sensory loss)
[i] Vision disorders (vision blurred, visual impairment, dry eye, photophobia, visual field defect, conjunctivitis, diplopia, eye pain, periorbital oedema, asthenopia, cataract, eye haematoma, photosensitivity reaction, visual acuity reduced, vitreous floaters, blepharospasm, cataract nuclear, colour blindness, eye infection, eye oedema, eye swelling, eyelid disorder, eyelid injury, eyelids pruritus, glaucoma, iridocyclitis, myopia, night blindness, ophthalmic herpes zoster, orbital oedema)
[j] Pneumonitis (pneumonitis, interstetial lung disease)
[k] Skeletal fractures (foot fracture, rib fracture, pathological fracture, acetabulum fracture, ankle fracture, femur fracture, fibula fracture, spinal compression fracture, sternal fracture, upper limb fracture)

Table 4: Adverse reactions occurring in paediatric patients ≤ 18 years old treated with AUGTYRO in CARE study*

		% All Grades	% ≥ 3 Grades
Infections and infestations			
Common	pneumonia	5.3	2.6
Blood and lymphatic system disorders			
Very common	anaemia	50.0	15.8
Metabolism and nutrition disorders			
Very common	increased appetite	13.2	0
	hyperkalaemia	10.5	0
	hyperuricaemia[a]	15.8	0
Nervous system disorders			
Very common	dizziness	21.1	0
	ataxia[b]	15.8	0
	cognitive disorders[c]	10.5	0
	paraesthesia	13.2	0
	sleep disorders[d]	18.4	2.6
	headache	31.6	0
	dysgeusia[e]	26.3	0
Common	peripheral sensory neuropathy[f]	5.3	0
Eye disorders			
Very common	vision disorders[g]	10.5	0

		% All Grades	% ≥ 3 Grades
Respiratory, thoracic and mediastinal disorders			
Very common	dyspnoea	15.8	2.6
	cough	26.3	0
Common	pleural effusion	5.3	2.6
Gastrointestinal disorders			
Very common	nausea	28.9	0
	vomiting	21.1	0
	constipation	39.5	2.6
	diarrhoea	18.4	5.3
	abdominal pain	15.8	2.6
Common	paraesthesia oral	7.9	0
Musculoskeletal and connective tissue disorders			
Very common	skeletal fractures[h]	18.4	5.3
	arthralgia	10.5	0
Common	myalgia	7.9	0
	muscular weakness	7.9	0
General disorders and administration site conditions			
Very common	pyrexia	26.3	0
	fatigue	36.8	2.6
Investigations			
Very common	blood creatine phosphokinase increased	15.8	0
	weight increased	26.3	15.8
	lymphocyte count decreased	18.4	0
	white blood cell count decreased	23.7	0
	neutrophil count decreased	21.1	2.6
	aspartate aminotransferase increased	23.7	2.6
	blood alkaline phosphatase increased	13.2	0
Injury, poisoning and procedural complications			
Common	fall	7.9	0

[a] Hyperuricaemia (hyperuricaemia, increased blood uric acid)
[b] Ataxia (gait disturbance, ataxia)
[c] Cognitive disorders (aphasia, confusional state, memory impairment, attention deficit hyperactivity disorder, depressed level of consciousness)
[d] Sleep disorders (somnolence, insomnia, obstructive sleep apnoea syndrome)
[e] Dysgeusia (dysgeusia, allodynia)
[f] Peripheral sensory neuropathy (peripheral sensory neuropathy, peripheral motor neuropathy)
[g] Vision disorders (vision blurred, eye pain, hemianopia homonymous, photophobia, visual impairment)
[h] Skeletal fractures (ankle fracture, foot fracture, stress fracture, fibula fracture, fracture, tibia fracture)
***** Frequencies include data from two adult patients

Description of selected adverse reactions

Dizziness
Among the 565 adult patients who received at least one dose of AUGTYRO in TRIDENT-1, dizziness (including dizziness, vertigo, dizziness postural, dizziness exertional, and vertigo positional) were reported in 65.5% (370/565) of patients; Grade 3 dizziness was reported 3.2% (18/565) of patients.

The median time to onset was 7 days (range: 1 day to 2.1 years). Resolution occurred in 187 patients (50.5%) with a median time to resolution of 40.0 weeks (range: 0.1 weeks to 323.6+ weeks). Dose reduction was required in 11.5% (65/565) of patients, and 10.3% (58/565) required dose interruption of AUGTYRO due to dizziness.

Ataxia
Ataxia (including ataxia, gait disturbances, balance disorder, cerebellar ataxia, and coordination abnormal) was reported in 29.0% (164/565) of patients; Grade 3 ataxia was reported in 0.5% (3/565) of patients. The median time to onset was 17 days (range: 1 day to 3.1 years). Resolution occurred in 85 patients (51.8%) with a median time to resolution of 28.4 weeks (range: 0.4+ weeks to 257.6+ weeks). Dose reduction was required in 7.6% (43/565) of patients, 5.0% (28/565) required dose interruptions and 0.2% (1/565) discontinued AUGTYRO due to ataxia.

Cognitive disorders
Cognitive disorders were reported in 22.3% (126/565) of patients. Cognitive disorders included memory impairment (12.2%), disturbance in attention (10.3%), cognitive disorder (6.2%), confusional state (2.1%), delirium (1.2%), amnesia (0.9%), attention deficit hyperactivity disorder, aphasia (0.7% each), depressed level of consciousness (0.5%), altered state of consciousness, neurological decompensation (0.4% each), bradyphrenia, delusion, dysgraphia, hallucinations, intellectual disability, mental disorder, and mental status change (0.2% each); Grade 3 cognitive disorders were reported in 1.2% (7/565) of patients. The median time to onset of cognitive disorders was 37 days (range: 1 day to 2.1 years). Resolution occurred in 56 patients (44.4%) with a median time to resolution of 69.3 weeks (range: 0.1 weeks to 235.7+ weeks). Dose reduction was required in 1.9% (11/565) of patients, 1.6% (9/565) required dose interruption and 0.9% (5/565) of patients discontinued AUGTYRO due to cognitive adverse reactions.

The incidences of reported CNS adverse reactions were similar in patients with or without CNS metastases.

Skeletal fractures
Skeletal fractures (including foot fracture, rib fracture, pathological fracture, acetabulum fracture, ankle fracture, femur fracture, fibula fracture, spinal compression fracture, sternal fracture, upper limb fracture) were reported in 3.5% (20/565) of patients; Grade 3 skeletal fractures were reported in 0.4% (2/565) of patients. The median time to onset was 5.6 months (range:10 days to 2.5 years). Resolution occurred in 10 patients (50.0%) with a median time to resolution of 40 weeks (range: 0.1 weeks to 220.9+ weeks). Dose interruption was required in 0.7% (4/565) of patients. Discontinuation of AUGTYRO was required in 0.2% (1/565) of patients due to skeletal fractures.

Skeletal fractures (including ankle fracture, foot fracture, fracture, stress fracture, tibia fracture and fibula fracture) was reported in 18.4% (7/38) of paediatric patients; Grade 3 skeletal fractures were reported in 5.3% (2/38) of paediatric patients. The median time to onset was 4.2 months (range: 25 days to 16.9 months). Resolution occurred in 57.1% (4/7) patients with a time to resolution 10 days-6.7 months. Dose interruption was required in 10.5% (4/38) of patients. Discontinuation of AUGTYRO was required in 2.6% (1/38) of paediatric patients due to skeletal fractures.

ILD/pneumonitis
Among the 565 patients treated with AUGTYRO, ILD/pneumonitis was reported in 3.2% (18/565) of patients; Grade 3 ILD/pneumonitis was reported in 0.9% (5/565) of patients. The median time to onset was 56 days (18 days to 11.7 months). Resolution occurred in 12 patients (66.7%) with median time to resolution 7.4 weeks (range: 0.6 weeks to 67.7 weeks). Dose interruption was required in 1.4% (8/565) of patients, 0.5% (3/565) of patients required dose reduction, and 0.9% (5/565) of patients permanently discontinued AUGTYRO due to ILD/pneumonitis.

Dyspnoea
Among the 565 patients treated with AUGTYRO, dyspnoea occurred in 31.3% (177/565) of patients, with Grade 3 in 5.1% (29/565). Median time to onset of dyspnoea was 43 days (range: 1 day to 2.1 years). Resolution occurred in 75 patients (42.4%) with median time to resolution 35.6 weeks (range: 0.1 weeks to 269.1+ weeks). Dose reduction was required in 1.6% (9/565) of patients, 6.5% (37/565) required dose interruptions and 1.1% (6/565) of patients were required to discontinue AUGTYRO due to dyspnoea.

Hepatotoxicity
Among the 565 patients treated with AUGTYRO, increased alanine transaminase (ALT) occurred in 22.1% (125/565) patients, increased aspartate aminotransferase (AST) occurred in 20.9% (118/565), including Grade 3 increased ALT in 1.8% (10/565) and increased AST in 2.5% (14/565). The median time to onset was 19 days (range: 1 day to 2.9 years). Resolution occurred in 120 patients (78.9%) with median time to resolution 5 weeks (0.7+ weeks to 92.0+ weeks). Dose interruption was required in 3% (17/565) of patients, 1.2% (7/565) of patients required dose reduction.

Vision disorder
Among the 565 patients who received AUGTYRO, vision changes occurred in 14.2 % (80/565) of patients, including Grade 3 vision disorder in 0.5% (3/565). Vision disorders included blurred vision (4.1%), visual impairment (2.3%), dry eye (1.6%). Resolution occurred in 34 patients (42.5%) with a range of time to resolution of 0.1 weeks to 226.9+ weeks. Dose interruption was required in 1.2% (7/565) of patients, 0.2% (1/565) of patients required dose reduction, and 0.2% (1/565) of patients permanently discontinued AUGTYRO due to vision disorders.

Muscular weakness
AUGTYRO can cause muscle weakness with or without creatine phosphokinase (CPK) elevation. Among the 565 patients treated with AUGTYRO, muscle weakness occurred in 21.6% (122/565) of patients, with Grade 3 in 1.9% (11/565). Median time to onset of muscle weakness was 39 days (range: 1 day to 3.4 years). Resolution occurred in 49 patients (40.2%) with median time to resolution 86.6 weeks (0.3 weeks to 236.6+ weeks). Dose interruption was required in 5.5% (31/565) of patients, 4.8% (27/565) of patients required dose reduction, and 0.9% (5/565) of patients permanently discontinued AUGTYRO due to muscle weakness.

Paediatric population

The safety of AUGTYRO was evaluated in 38 paediatric patients (including 22 paediatric patients < 12 years of age, 14 paediatric patients 12-17 years of age and 2 patients ≥ 18 years of age) with advanced or metastatic tumours harbouring *ALK*, *ROS1*, or *NTRK1-3* gene fusions in the phase I/II, open-label, single-arm, multicentre, multicohort CARE study. Of the 14 patients between the age of 12 and 17, 7 patients were *NTRK* positive.

Adverse reactions observed in paediatric patients were comparable in frequency and intensity to those observed in adults except skeletal fractures which were observed at a higher frequency in paediatric patients (18.4%) compared to adults (3.5%). No differences in the spectrum of adverse reactions reported in adults and the paediatric population were evident with no new or unexpected adverse reactions observed. The events reported in the adult population can also be observed in children and adolescents. The most frequent adverse reactions in paediatric patients were constipation, fatigue and headache. The most frequent Grade ≥ 3 adverse reactions in paediatric patients were weight increased, diarrhoea, and skeletal fractures.

Elderly

Of the 565 patients who received AUGTYRO 25% were 65 years or older, and 6% were 75 years of age or older. The frequency of adverse reactions was generally similar for patients < 65 years of age and patients ≥ 65 years of age. The frequencies of serious adverse reactions were higher in patients 65-75 years of age (48%) and ≥ 75 years of age (63%) compared to patients 18-65 years of age (37%). The most common serious adverse reactions in patients ≥ 65 years of age were pneumonia, dyspnoea, and pleural effusion. The rate of discontinuations was higher in patients 65-75 years of age (16%) and ≥ 75 years of age (23%) compared to patients 18-65 years of age (9%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

There is limited experience of overdose with AUGTYRO. Symptoms of overdose are not established. In the event of overdose, physicians should follow general supportive measures and treat symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EX28

Mechanism of action

Repotrectinib is an inhibitor of proto-oncogene tyrosine-protein kinase ROS1, the tropomyosin receptor tyrosine kinases (TRK) TRKA, TRKB, TRKC, and anaplastic lymphoma kinase (ALK) with IC50 values of 0.05 to 1.04 nM.

Fusion proteins that include ROS1 or TRK domains can drive tumourigenic potential through hyperactivation of downstream signalling pathways leading to unconstrained cell proliferation. Repotrectinib has demonstrated *in vitro* and *in vivo* inhibition of cell lines expressing the targeted fusion oncogenes ROS1, TRKA, TRKB, TRKC, and corresponding mutations ($ROS1^{G2032R}$, $ROS1^{D2033N}$, $TRKA^{G595R}$, $TRKB^{G639R}$, $TRKC^{G623R}$). Repotrectinib binds inside the boundary of the ATP-binding pocket and avoids steric interference from both solvent front and gatekeeper mutations.

Cardiac Electrophysiology

Analysis of ECG data from 334 patients in the TRIDENT-1 phase 2 study, who received AUGTYRO at the recommended dose (unknown prandial state), demonstrated that the upper limit of 90% confidence interval (CI) of the mean QTcF change from baseline (ΔQTcF) exceeded 10 milliseconds (ms) for a few time point estimates but remained < 20 ms.

Patients with increased risk of QTc prolongation were not enrolled in TRIDENT-1.

Clinical efficacy and safety

The efficacy of repotrectinib was evaluated in adult patients with solid tumours harboring *ROS1* or *NTRK1-3* rearrangements in a phase I /II, multicentre, single-arm, open-label, multi-cohort clinical study (TRIDENT-1). Patients received various doses and schedules of repotrectinib (156 [91%] received repotrectinib 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).

The primary efficacy endpoint was overall response rate (ORR) by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. The secondary endpoints were duration of response (DOR), progression free survival (PFS) by BICR according to RECIST v1.1 and overall survival (OS). Intracranial response according to modified RECIST v1.1 was assessed by BICR. Tumour assessments with imaging were performed at least every 8 weeks.

ROS1-positive NSCLC

The efficacy of repotrectinib was evaluated in a subgroup of adult patients with locally advanced or metastatic *ROS1*-positive NSCLC pooled from phase I/II of TRIDENT-1. Patients were required to have ECOG performance status ≤ 1, measurable disease per RECIST v 1.1, ≥ 8 months follow-up

from first dose. Identification of *ROS1* 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* fusions were identified by NGS in 57%, FISH in 22%, and PCR in 21% of patients. All patients were assessed for CNS lesions at baseline.

Among the 121 ROS1 inhibitor naïve patients, the median age was 57 years (range: 28 – 93), 23% and 5% were 65 years or older and 75 years or older respectively. The majority were female (56%) Asian (60%) or White (30%); and never smoked (63%). Baseline ECOG performance status was 0 (38%) and 1 (62%). At baseline, 92% of patients had metastatic disease, 25% of patients had CNS metastases by BICR; 97% of patients had adenocarcinoma; 26% of patients had prior platinum-based chemotherapy for locally advanced or metastatic disease.

Among the 107 patients who had received 1 prior ROS1 TKI (crizotinib 77%, entrectinib 21%, and ceritinib 3%) with no prior platinum-based chemotherapy, the median age was 57 years, (range: 33-81), 29% and 8% were 65 years or older and 75 years or older, respectively. The majority were female (74%), Asian (42%) or White (49%); never smoked (68%); and ECOG performance status of 0 (34%) and 1 at baseline (66%). At baseline, 98% patients had metastatic disease, 40% had CNS metastases by BICR, and 96% had adenocarcinoma.

Efficacy results are summarised in Table 5.

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

Efficacy parameters	**ROS1 inhibitor naïve patients (N = 121)**	**ROS1 inhibitor pretreated patients (N = 107)**
Confirmed Overall Response Rate, % (95% CI)	77 (68, 84)	49 (39, 59)
Complete Response Rate N (%)	15 (12)	8 (8)
Partial Response Rate N (%)	78 (65)	44 (41)
Median Duration of Response (mDOR) in Months (95% CI)	33.6 (25.5, NE)	14.8 (7.6, NE)
Range (months)	1.4+ – 49.7+	1.8+ – 31.4
12-months durable response % (95% CI)	77 (68, 86)	53 (38, 68)
18-months durable response % (95% CI)	70 (60, 80)	44 (27, 61)
24-months durable response % (95% CI)	64 (52, 75)	38 (19, 56)

DOR landmarks are by K-M estimates.
Minimum follow up was 7 months.
+denotes ongoing response.
NE : Not Estimated

The median time to response was 1.84 (range 1.5, 7.4) months for TKI-naïve patients and 1.84 (range 1.6, 22.1) months for TKI pretreated patients.

Among the 121 TKI naive patients, 14 had measurable CNS metastases at baseline as assessed by BICR (4 patients had CNS intervention within 60 days of first dose of study treatment), and intracranial response was observed in 12 patients (3 CR and 9 PR), for an intracranial ORR of 86% (95% CI: 57, 98). Among the 107 TKI pretreated patients with no prior platinum-based chemotherapy,23 had measurable CNS metastases at baseline as assessed by BICR (7 patients had CNS intervention within 60 days of first dose of study treatment), and intracranial response was observed in 10 patients (2 CR and 8 PR), for an intracranial ORR of 44% (95% CI: 23, 66).

In35 ROS1 TKI pretreated patients with solvent front mutation, ORR was 51.4% (95% CI: 34.0, 68.6).

NTRK *gene-fusion-positive solid tumours*

The efficacy of repotrectinib was evaluated in a population of patients with locally advanced (not eligible for surgery, radiation or multimodality therapy) or metastatic *NTRK* gene fusion positive solid tumours pooled from phase I /II. Patients were required to have ECOG performance status ≤ 1, and measurable disease per RECIST v 1.1 and ≥ 8 months follow-up from first dose. Identification of *NTRK* gene fusions in tumour specimens was prospectively determined in local laboratories using NGS, PCR or FISH tests. All *NTRK 1-3* gene fusion positive tumours by local FISH testing required central laboratory confirmation using an analytically validated NGS test. *NTRK* fusions were identified by NGS in 96%, FISH in 2.5%, and PCR in 1.7% of patients. All patients were assessed for CNS lesions at baseline.

Among the 51 TKI-naive patients in phase I/II, the median age was 61 years (range: 25–84); 41% and 12% were 65 years or older and 75 years or older respectively. The majority were female (53%); Asian (51%) or White (25%). Baseline ECOG performance status was 0 (45%) and 1 (55%). At baseline, 96% of patients had metastatic disease and 20% patients had CNS metastases by BICR. The most common tumours were NSCLC 53%, thyroid cancer 12%, salivary gland cancer 10%, and soft tissue sarcoma 6%.

Among the 69 TKI-pretreated patients in phase I/II, 17% of patients had received 2 prior TKI therapies, 52% of patients had received larotrectinib and 46% entrectinib, the median age was 56 years (range: 18–81); 36% and 7% were 65 years or older and 75 years or older respectively. The patients were female (48%); Asian (30%) or White (58%). Baseline ECOG performance status was 0 (39%) and 1 (61%). At baseline, 91% of patients had metastatic disease and 23% of patients had CNS metastases by BICR. The most common tumours were NSCLC 25%, salivary gland cancer 17%, soft tissue sarcoma 15%, and thyroid cancer 10%.

ORR and DOR were assessed by BICR and according to RECIST v1.1. Intracranial response according to modified RECIST v1.1 was assessed by BICR. Tumour assessments with imaging were performed at least every 8 weeks. The primary efficacy populations included 51 TKI inhibitor naïve patients and 69 patients who had received 1 prior TKI inhibitor. Efficacy results with a minimum follow-up of 8 months are summarised in Table 6.

Table 6: Overall efficacy by BICR in adults with *NTRK* gene fusion-positive tumours

Efficacy parameters	**TKI naïve patients (n = 51)**	**TKI pretreated patients (n = 69)**
Confirmed Overall Response Rate, % (95% CI)	59 (44, 72)	48 (36, 60)
Complete Response N (%)	8 (16)	2 (3)
Partial Response N (%)	22 (43)	31 (45)
Median Duration of Response in Months (95% CI)	NE (NE, NE)	9.8 (7.36, 12.98)
Range (months)	0.0+, 43.9+	1.8, 26.5+
6-months durable response % (95% CI)	92.9 (83.3, 100.0)	72.7 (57.5, 87.9)
9-months durable response % (95% CI)	89.1 (77.5, 100.0)	62.8 (46.0, 79.6)
12-months durable response % (95% CI)	89.1 (77.5, 100.0)	41.6 (23.8, 59.3)

95% CIs are based on Kaplan-Meier methodology using the Greenwood variance estimate
DOR landmarks are by K-M estimates
Minimum follow up was 8 months
+denotes ongoing response
NE : Not Estimated

The median time to response was 1.8 (range 1.6, 7.3) months for TKI-naïve patients and 1.9 (range 1.7, 3.7) months for TKI pretreated patients.

In 30 NTRK TKI pretreated patients with solvent front mutation at baseline, ORR was 53% (95% CI: 34.3,71.7).

ORR and DOR by tumour type in adult patients with *NTRK* gene fusion-positive solid tumours are presented in Table 7 below.

Table 7: Efficacy results in TKI naive *NTRK* gene fusion-positive solid tumours

Tumour type	**Patients (N = 51)**	**ORR**		**DOR**
		n (%)	**95% CI**	**Range (months)**
NSCLC	27	17 (63.0)	42.4, 80.6	0.0+, 31.3+
Thyroid Cancer	6	6 (100.0)	54.1, 100.0	4.7, 43.9+
Salivary Gland Cancer	5	4 (80.0)	28.4, 99.5	12.9+, 31.4+
Sarcoma, Soft tissue	3	1 (33.3)	0.8, 90.6	14.7+
Other*	3	SD, SD, SD	NA	NA
Colorectal cancer	2	CR, SD	NA	7.5+
Breast Cancer	2	PD, PD	NA	NA
Glioblastoma	1	SD	NA	NA
Cholangiocarcinoma	1	PD	NA	NA
Peripheral Nerve Sheath Tumour	1	PR	NA	23.0+

*Includes oesophageal cancer, prostate cancer and head and neck cancer
PD: progressive disease; PR: partial response; SD: stable disease; NA: not applicable
+denotes ongoing response

Table 8: Efficacy results in TKI pretreated *NTRK* gene fusion-positive solid tumours

Tumour type	**Patients (N = 69)**	**ORR**		**DOR**
		n (%)	**95% CI**	**Range (months)**
NSCLC	17	9 (52.9)	27.8, 77.0	1.9, 23.0+
Salivary Gland Cancer	12	9 (75.0)	42.8, 94.5	3.7, 26.5+
Sarcoma, Soft tissue	10	1 (10.0)	0.3, 44.5	5.6
Thyroid Cancer	7	2 (28.6)	3.7, 71.0	2.0, 9.6
Other*	5	2 (40.0)	5.3, 85.3	11.0+, 14.8+
Colorectal cancer	4	2 (50.0)	6.8, 93.2	9.2, 17.5
Glioblastoma	3	1 (33.3)	0.8, 90.6	23.5
Neuroendocrine Tumour	3	3 (100.0)	29.2, 100.0	5.5, 9.1
Pancreatic Cancer	3	PD, PD, SD	NA	NA
Cholangiocarcinoma	2	PR, PD	NA	1.8
Peripheral Nerve Sheath Tumour	2	PR, PR	NA	5.5, 11.1
Breast Cancer	1	PR	NA	15.6+

* Include gallbladder cancer, cervical cancer, gastrointestinal stromal tumour, mucoepidermoid and unknown primary cancer
PD: progressive disease; PR: partial response; SD: stable disease; NA: not applicable
+denotes ongoing response

Due to the rarity of *NTRK* gene fusion-positive cancers, patients were studied across multiple tumour types with limited numbers of patients in some tumour types, causing uncertainty in the ORR estimate per tumour type. The ORR in the total population may not reflect the expected response in a specific tumour type.

AUGTYRO was evaluated in paediatric patients with locally advanced or metastatic tumours harbouring *NTRK* alteration in the phase I/II, open-label, single-arm, multicentre, multicohort CARE study. Efficacy was evaluated in patients who received AUGTYRO orally either as 160 mg once daily,

or 160 mg once daily for 14 days followed by 160 mg twice daily or adult equivalent dose, until disease progression or unacceptable toxicity.

Patients were required to have Lansky (< 16 years) or Karnofsky (≥ 16 years) score of at least 50, and measurable disease per RECIST v1.1 or Response Assessment in Neuro-Oncology Criteria (RANO). Patients with a primary CNS tumour or CNS metastases were required to be neurologically stable and on a stable or decreasing dose of steroids for at least 14 days prior to enrolment.

Identification of *NTRK1-3* gene fusions in tumour specimens was prospectively determined in local laboratories using NGS, PCR or FISH tests. All *NTRK* gene fusion positive tumours by local FISH testing require retrospective central laboratory confirmation using an analytically validated NGS test.

Primary efficacy endpoints were ORR by BICR according to RECIST v1.1 or RANO and secondary efficacy endpoints were DOR and PFS by BICR according to RECIST v1.1 or RANO and OS. Tumour assessments with imaging were performed at least every 8 weeks.

Thirteen *NTRK* positive paediatric patients (age range: 1 year to 15 years old; 5 were 12-17 years of age), had measurable disease at baseline per BICR and at least one post baseline scan were evaluated in CARE study. Of these, 5 were NTRK TKI naive (3 CNS tumours and 2 solid tumours) and 8 had received prior NTRK TKI therapy (3 CNS tumours and 5 solid tumours).

Of the 5 TKI naïve patients, 1 complete response and 2 partial responses were observed. Among the 8 TKI-pretreated patients, there were 2 partial responses.

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with AUGTYRO in one or more subsets of the paediatric population in the treatment with *NTRK* gene fusion-positive locally advanced or metastatic solid tumours (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetic (PK) parameters for repotrectinib have been characterised in patients with *NTRK* gene fusion-positive solid tumours, *ROS1*-positive NSCLC, and in healthy subjects. Repotrectinib maximum concentration ($C_{max)}$ and area under the curve over time to infinity ($AUC_{0\text{-}inf}$) increases were 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. Steady state PK was time-dependent due to autoinduction of CYP3A4. The steady-state average concentration (C_{avg}) of 160 mg twice daily dosing regimen is similar to C_{avg} following 160 mg single dose administration.

Repotrectinib estimated steady state geometric mean (CV%) C_{max} is 572 ng/mL (38.3%), C_{min} is 158 ng/mL (57.7%), and C_{avg} ($AUC_{0\text{-}12h}$ divided by dosing interval) is 347 ng/mL (42.3%) for 160 mg twice a day.

Absorption

Following oral administration of ascending single doses of repotrectinib ranging from 40 mg to 240 mg, repotrectinib exhibited rapid absorption with C_{max} occurring at approximately 2-3 hours post

dose under fasted conditions. The geometric mean (CV%) absolute bioavailability of repotrectinib is 45.7% (19.6%).

A high-fat, high-calorie meal (916 calories, 56% fat) increased repotrectinib $AUC_{0\text{-}inf}$ by 56% and C_{max} by 149% following a single 160 mg oral dose (administered as 40 mg capsules). In another study, a high-fat, high-calorie meal increased $AUC_{0\text{-}inf}$ by 42% and C_{max} by 110% following a single 160 mg oral dose (administered as 160 mg capsules). Similar increases ($AUC_{0\text{-}inf}$ by 36% and C_{max} by 124%) were observed with a low-fat, low-calorie meal.

Repotrectinib peak concentration occurred at approximately 4 to 6 hours post a single oral dose of 40 mg to 160 mg under fed conditions (high-fat meal).

Distribution

Binding of repotrectinib to human plasma protein was 95.4% *in vitro*. The blood-to-plasma ratio was 0.56 *in vitro*. The geometric mean (CV%) apparent volume of distribution (V_z/F) was 432 L (55.9%) in cancer patients following a single 160 mg oral dose of repotrectinib.

Biotransformation

Repotrectinib is primarily metabolised by CYP3A4 to form hydroxylated metabolites followed by secondary glucuronidation. No metabolite exceeded 10% of total circulating drug-related radioactivity.

Elimination

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

The geometric mean (CV%) apparent oral clearance (CL/F) was 15.9 L/h (45.5%) in cancer patients following a single 160 mg oral dose of repotrectinib. Based on the population PK (popPK) analysis, the single dose mean (SD) terminal half-life ($t_{1/2}$) was estimated to be 68.6 (29.6) hours, and the steady state terminal $t_{1/2}$ was estimated to be 44.5 (20.8) hours in cancer patients.

Following a single oral 160 mg dose of [^{14}C] repotrectinib, 4.84% (0.56% as unchanged) of the radioactivity was recovered in urine and 88.8% (50.6% as unchanged) in faeces.

Pharmacokinetics in special populations

Renal impairment
In the popPK analysis, mild (eGFR-CKD-EPI 60 to 90 mL/min, n = 139) or moderate (eGFR-CKD-EPI 30 to 60 mL/min, n = 27) renal impairment did not influence the clearance of repotrectinib. Repotrectinib has not been studied in patients with severe renal impairment (eGFR- CKD-EPI < 30 mL/min).

Hepatic impairment
In the popPK analysis, mild hepatic impairment (total bilirubin > 1.0 to 1.5 times ULN or AST >ULN, n = 59) did not influence the clearance of repotrectinib. Pharmacokinetics of repotrectinib have not been established in patients with moderate (total bilirubin > 1.5 to 3 times ULN) or severe (total bilirubin > 3 times ULN) hepatic impairment.

Effects of age, body weight, race and gender
In the popPK analysis, no clinically relevant differences in the pharmacokinetics of repotrectinib were identified based on gender, age (18 years to 93 years), body weight (39.5 kg to 169 kg), or race (Asian and White) in adults.

Paediatrics
PK data was available from paediatric patients 12 years and older (n = 13, age 13 to 15 years, body weight 46.4 to 76.7 kg). Based on popPK simulations, adolescents 12 years and older have similar

systemic exposure as that of adults when administered the adult dose of 160 mg once daily for 14 days, followed by 160 mg twice daily.

In vitro studies
CYP Enzymes: Repotrectinib induces CYP3A4, CYP2B6, CYP2C8, CYP2C19, CYP2C9 and inhibits CYP3A4/5 (GI tract), CYP2C8 and CYP2C9.

Other Metabolic Pathways: Repotrectinib inhibits UGT1A1.

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

5.3 Preclinical safety data

Carcinogenicity

Carcinogenicity studies with repotrectinib were not conducted.

Genotoxicity

Repotrectinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay.

Repotrectinib caused micronuclei formations *via* an aneugenic mechanism in human lymphoblastoid TK6 cells *in vitro*, and in bone marrow of rats *in vivo* at doses > 100 mg/kg nominal dose. The exposure of animals at the no observed effect level (NOEL) for aneugenicity was approximately 3.4-fold human exposure at the recommended clinical dose (based on AUC).

Reproductive toxicity

In a preliminary embryo-foetal development study in rats, teratogenic and embryo-foetal effects (foetal external malformation of malrotated hindlimbs and decreased foetal weight) and maternal effects (skin scabbing and abrasions in cervical and thoracic regions and increased body weight) were observed in pregnant rats at exposures that were less than 2-fold human exposure at the recommended clinical dose.

Dedicated fertility studies were not conducted with repotrectinib. 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 in rats of up to 2-fold and 2.6-fold in males and females, respectively, and exposures in monkeys that were below the human exposure at the recommended clinical dose.

Repeat dose toxicity studies

Following repeat-dose oral administration of repotrectinib daily for up to 3 months, the main toxicities observed in rats at exposure levels < 3-fold human exposure were skin scabs/ulcerations, CNS effects (i.e. ataxia, tremors), decreased RBC parameters, and bone marrow hypocellularity.

The main toxicities observed in monkeys at exposure margins below clinical exposure were emesis, watery faeces, minimal subacute/chronic inflammation and/or minimal to mild mucosal gland hyperplasia in the large intestines, and decreased RBC parameters. The skin ulcerations were considered secondary to NTRK inhibition resulting in loss of sensation and bodily injury.

Juvenile rat toxicity studies

Overall, juvenile rats were dosed and evaluated up to 58 days (starting on postnatal day [PND] 12 through PND 70) in repeat-dose toxicity studies. CNS-related mortality was observed at PND 13 to PND 15 (approximately equivalent to infant) at exposure levels ≥ 1.5-fold adolescent human exposure.

Decreased effects on growth (decreased body weight, food consumption and femur length) were observed at exposure levels ≥ 0.1-fold the adolescent human exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Microcrystalline cellulose
Sodium lauryl sulphate
Croscarmellose sodium
Silica colloidal anhydrous
Magnesium stearate (for 160 mg hard capsule only)

Capsule shell

Gelatin
Titanium dioxide (E171)
Brilliant blue (E133 - for 160 mg hard capsule only)

Printing ink (40 mg hard capsule)

Shellac (E904)
Indigo carmine aluminium lake (E132)

Printing ink (160 mg hard capsule)

Shellac (E904)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

AUGTYRO 40 mg hard capsules

High-density polyethylene (HDPE) bottles with 2-piece child-resistant continuous thread (CRCT) polypropylene (PP) closures.

Each bottle contains 60 hard capsules packed in a cardboard carton.
Each bottle contains 120 hard capsules packed in a cardboard carton.

Each carton contains one bottle.

AUGTYRO 160 mg hard capsules

PVC/polychlorotrifluoroethylene clear blister with push through aluminium foil lidding.

Packs of 20 or 60 hard capsules with 10 hard capsules in blister cards.

Not all pack sized may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Augtyro 40 mg hard capsules
EU/1/24/1883/001 (60 capsules)
EU/1/24/1883/002 (120 capsules)

Augtyro 160 mg hard capsules
EU/1/24/1883/003 (20 capsules)
EU/1/24/1883/004 (60 capsules)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Swords Laboratories Unlimited Company
T/A Bristol-Myers Squibb Pharmaceutical Operations
External Manufacturing
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm histology-independent efficacy, efficacy despite resistance mutations, and IC responses of repotrectinib in adults, the MAH should submit the final CSR of the ongoing phase 1/2 trial TRIDENT-1 (all cohorts).	Q1 2029
In order to further investigate the efficacy and long-term safety in paediatric patients with solid tumours expressing a NTRK gene fusion, the MAH should submit the results of the final safety and efficacy analysis of the ongoing Phase 1/2, Open-label, Safety, Tolerability, Pharmacokinetics, and Anti-tumour Activity Study of repotrectinib in Paediatric and Young Adult Subjects with Advanced or Metastatic Malignancies Harboring ALK, ROS1, or NTRK1-3 Alterations (CARE).	Q4 2030

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

AUGTYRO 40 mg hard capsules
repotrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 40 mg repotrectinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

hard capsule

60 hard capsules
120 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1883/001
EU/1/24/1883/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

AUGTYRO 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

AUGTYRO 40 mg hard capsules
repotrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 40 mg repotrectinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

hard capsule

60 hard capsules
120 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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EU/1/24/1883/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

AUGTYRO 160 mg hard capsules
repotrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 160 mg repotrectinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

hard capsule

20 hard capsules
60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1883/003
EU/1/24/1883/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

AUGTYRO 160 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

AUGTYRO 160 mg capsules
repotrectinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

AUGTYRO 40 mg hard capsules
AUGTYRO 160 mg hard capsules
repotrectinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What AUGTYRO is and what it is used for

What AUGTYRO is
AUGTYRO is a cancer medicine that contains the active substance repotrectinib.

What AUGTYRO is used for

AUGTYRO is used to treat either:
- adults with a type of lung cancer called 'non-small cell lung cancer' (NSCLC) that is caused by a change in the *ROS1* gene or,
- adults and children 12 years of age and older with solid tumour (cancer) in various parts of the body that is caused by a change in the *NTRK* gene.

ROS1-positive non-small cell lung cancer

AUGTYRO is used when:
- a test has shown that your cancer cells have a change in a gene called '*ROS1*' (see 'How AUGTYRO works' below), and
- your cancer is advanced – for example, has spread to other parts of your body (metastatic).

NTRK gene fusion-positive solid tumour cancer

AUGTYRO is used when:
- a test has shown that your cancer cells have a change in a gene called '*NTRK*' and has spread within the affected organ or to other organs in your body, or if surgery to remove

the cancer is likely to result in severe complications (see 'How AUGTYRO works' below), and
- you have received prior treatment with medicines called NTRK inhibitors, or
- you have not received treatment with medicines called NTRK inhibitors and other treatments are not suitable for you.

How AUGTYRO works

AUGTYRO works by blocking the action of proteins that do not work properly as a result of changes in the *NTRK* or *ROS1* genes that make them. These abnormal proteins can cause cancer cells to grow uncontrollably. By blocking the abnormal proteins, AUGTYRO may slow or stop cancer cell growth and may help shrink your cancer.

2. What you need to know before you take AUGTYRO

Do not take AUGTYRO
- if you are allergic to repotrectinib or any of the other ingredients of this medicine (listed in section 6).

If you are not sure, talk to your doctor, pharmacist or nurse before taking AUGTYRO.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking AUGTYRO if
- you have recently experienced dizziness, memory loss, confusion, hallucinations, mental status changes, loss of muscle coordination, or uncoordinated or unsteady walking.
- you have ever had any other lung problems. Tell your doctor right away if you have any new or worsening symptoms including shortness of breath, or cough, or fever.
- you have a history of fractured bones, or condition which may increase your risk of breaking bones.
- if you have liver problems.

Other medicines and AUGTYRO
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines for:
- Acquired Immune Deficiency Syndrome (AIDS)/Human immunodeficiency virus (HIV) infection – such as ritonavir, saquinavir, efavirenz
- fungal infections (anti-fungals) – such as ketoconazole, itraconazole, voriconazole, posaconazole
- stopping seizures or fits (anti-epileptics) – such as carbamazepine or phenytoin
- tuberculosis – such as rifampicin
- depression – such as bupropion, fluvoxamine, or an herbal medicine St. John's Wort (*Hypericum perforatum*)
- cancers – such as apalutamide, everolimus
- suppressing your body's immune system, or prevent the body from rejecting an organ transplant – such as sirolimus, tacrolimus, cyclosporin, sulfasalazine
- inflammed joints or joint autoimmune disease (rheumatoid arthritis) – methotrexate
- severe pain – such as alfentanil, fentanyl
- high blood pressure – such as verapamil, nifedipine, felodipine, valsartan
- lowering blood cholesterol – such as lovastatin, simvastatin, rosuvastatin
- lowering blood sugar levels – such as repaglinide, tolbutamide, metformin
- gastric reflux (heartburn) – such as cisapride, omeprazole
- preventing formation of blood clots – such as warfarin, dabigatran etexilate
- heart problems – such as digoxin, edoxaban

- allergies – such as fexofenadine
- birth control – if you are using hormonal oral contraceptives, you must also use a reliable barrier method of contraception (see Pregnancy and breast-feeding).

AUGTYRO with food and drink
Do not drink grapefruit juice or eat grapefruit or Seville oranges during your treatment with AUGTYRO. It may increase the amount of the medicine in your blood to a harmful level.

Pregnancy and breast-feeding

Women and contraception

You should avoid becoming pregnant while taking this medicine because it could harm the baby. If you are able to become pregnant, you must use highly effective contraception while on treatment and for at least 2 months after stopping treatment.

It is not known if AUGTYRO can reduce the effect of birth control medicines (pills or implanted hormonal contraceptives). If you use hormonal birth control, you should use an additional reliable non-hormonal method of birth control such as a barrier method (e.g. condom) so you do not become pregnant while you are taking AUGTYRO and for 2 months after you stop treatment.

Talk to your doctor about the right methods of contraception for you and your partner.

Men and contraception

Your female partner should avoid becoming pregnant while you are taking this medicine because it could harm the baby. If your female partner is able to become pregnant, you should use condoms while on treatment and for at least 4 months after stopping treatment.

Talk to your doctor about the right methods of contraception for you and your partner.

Pregnancy

- Do not take AUGTYRO if you are pregnant. This is because it may harm your baby.
- If you are a woman who can become pregnant, your doctor will arrange pregnancy testing for you before you start treatment with AUGTYRO.
- If you become pregnant when taking the medicine or during the 2 months after taking your last dose, tell your doctor right away.

Breast-feeding

Do not breast-feed while taking this medicine. This is because it is not known if AUGTYRO can pass over into breast milk and could therefore harm your baby.

Driving and using machines
AUGTYRO may affect your ability to drive or use machines. AUGTYRO may cause you to:
- feel dizzy
- impaired balance or coordination
- pass out (lose consciousness)
- feel tired
- have changes in your mental status, feel confused or see things that are not there (hallucinations)
- have blurred vision

If this happens, you should not drive, use a bicycle, or use machines until your symptoms resolve. Talk to your doctor or pharmacist about whether it is okay for you to drive, cycle or use machines.

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

3. How to take AUGTYRO

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
The recommended dose is 160 mg once a day for the first 14 days, followed by 160 mg twice a day until your doctor tells you otherwise.

Depending on how you respond to the treatment, your doctor may suggest a lower dose, or even stopping treatment briefly. For lower doses, you may need to take a dose of 120 mg (three 40 mg capsules) or a dose of 80 mg (two 40 mg capsules).

Always take this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse have told you. Check with your doctor, pharmacist or nurse if you are not sure.

How to take AUGTYRO
Take AUGTYRO by mouth – with or without food. Swallow each capsule whole. Do not open, crush, chew or dissolve the contents of the capsules.

If you take more AUGTYRO than you should
If you take more AUGTYRO than you should, talk to a doctor or go to hospital straight away. Take the medicine pack and this leaflet with you.

If you forget to take AUGTYRO
If you missed a dose or vomited after taking a dose, take the next dose as prescribed. Do not take a double dose to make up for a missed dose.

If you stop taking AUGTYRO
Do not stop taking this medicine without talking to your doctor first. It is important to take AUGTYRO every day for as long as your doctor prescribes it for you. If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor right away if you notice any of the following after having taken AUGTYRO:
- you feel dizzy, confused, have changes in mood, hallucinations (see things that are not there) or memory problems (cognitive disorders), or lose muscle coordination, walk uncoordinatedly or unsteadily (ataxia)
- you have shortness of breath (dyspnoea), cough, fever (pyrexia) or, disorders causing scarring in the lungs
- you notice any joint pain, bone pain, deformities or changes in your ability to move, as this may be a sign of fractures

Your doctor may lower your dose, stop your treatment for a short time or stop your treatment completely.

Other side effects include

Adults

Very common side effects (may affect more than 1 in 10 people):

- infection of the lungs
- decrease in the number of healthy red blood cells that carry oxygen around the body (anaemia)
- dizziness
- loss of muscle coordination, being unsteady when walking (ataxia)
- major change in thinking patterns (cognitive disorders)
- sensations like numbness and tingling (paraesthesia)
- inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning (peripheral sensory neuropathy)
- sleep disorders
- headache
- taste change (dysgeusia)
- seeing flashes of light, blurred vision, light sensitivity, floaters or double vision (vision disorder)
- shortness of breath
- cough
- urge to vomit (nausea)
- vomiting
- constipation
- diarrhoea
- muscular weakness
- leg and/or arm pain
- joint pain (arthralgia)
- muscle pain (myalgia)
- back pain
- fever
- feeling tired (fatigue)
- decreased appetite
- swelling of ankles, feet and hands
- increased blood level of enzyme (creatine phosphokinase) from muscle
- weight gain
- increased amounts of the liver enzymes aspartate aminotransferase or alanine aminotransferase

Common side effects (may affect up to 1 in 10 people)

- increased blood level of enzyme (uric acid) (hyperuricaemia)
- inflammation and disorders causing scarring in the lungs
- fluid around lungs (pleural effusion)
- pain in the abdomen
- bone fractures
- increased amount of the liver enzymes gamma-glutamyltransferase or alkaline phosphatase in your blood
- decreased number of a type of white blood cells called lymphocyte
- decreased level of white blood cells
- decreased number of a type of white blood cell called neutrophil
- fall

Patients 18 years or younger

Very common side effects (may affect more than 1 in 10 people):

- decrease in the number of healthy red blood cells that carry oxygen around the body (anaemia)
- increased appetite
- high blood levels of potassium
- increased blood level of enzyme (uric acid) (hyperuricaemia)
- dizziness
- loss of muscle coordination, being unsteady when walking (ataxia)
- major change in thinking patterns (cognitive disorders)
- sensations like numbness and tingling (paraesthesia)
- sleep disorders
- headache
- taste change (dysgeusia)
- seeing flashes of light, blurred vision, light sensitivity, floaters or double vision, (vision disorder)
- shortness of breath
- cough
- urge to vomit (nausea)
- vomiting
- constipation
- diarrhoea
- pain in abdomen
- bone fractures
- joint pain (arthralgia)
- fever
- feeling tired (fatigue)
- increased blood level of enzyme (creatine phosphokinase) from muscle
- weight gain
- decreased number of white blood cells called lymphocytes
- decreased number of a type of white blood cells
- decreased number of a type of white blood cells called neutrophils
- increased amounts of the liver enzymes aspartate aminotransferase or alkaline phosphatase in your blood

Common side effects (may affect up to 1 in 10 people)

- infection of lungs
- inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning (peripheral sensory neuropathy)
- fluid around lungs (pleural effusion)
- sensations like numbness and tingling on the lips, tongue, or entire mouth (paraesthesia oral), muscle pain (myalgia)
- muscular weakness
- fall

Reporting of side effects

If you get any side effects, talk to your doctor or, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store AUGTYRO

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, bottle or blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What AUGTYRO contains
The active substance is repotrectinib.
AUGTYRO 40 mg: each capsule contains 40 mg repotrectinib
AUGTYRO 160 mg: each capsule contains 160 mg repotrectinib

The other ingredients are:
- *Capsule content*: Microcrystalline cellulose, sodium lauryl sulphate, croscarmellose sodium, silica, colloidal anhydrous, and magnesium stearate (160 mg hard capsules only) (see section 2).
- *Capsule shell*: Gelatin, titanium dioxide (E171), brilliant blue (E133 - 160 mg hard capsules only).
- Printing ink (40 mg hard capsules): Shellac (E904) and indigo carmine aluminium lake (E132)
- Printing ink (160 mg hard capsules): Shellac and titanium dioxide.

What AUGTYRO looks like and contents of the pack
AUGTYRO 40 mg hard capsules (capsules) are opaque white with ‘REP 40’ imprinted in blue.
AUGTYRO 160 mg hard capsules (capsules) are opaque blue with ‘REP 160’ imprinted in white.

AUGTYRO 40 mg is provided in carton containing one bottle with either 60 or 120 hard capsules.
AUGTYRO 160 mg is packaged in blister cards containing 10 hard capsules. Each pack contains either 20 or 60 hard capsules.

Not all pack sizes may be marketed.

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.