PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrALUNBRIG®

Brigatinib Tablets

Tablet, 30 mg, 90 mg, and 180 mg, Oral

Protein Kinase Inhibitor (L01XE)

Takeda Canada Inc.
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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, General, Drug Interactions and Reproductive Health: Female and male Potential	07/2022
9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions	07/2022
14 CLINICAL TRIALS, 14.2 Study Results	07/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ALUNBRIG (brigatinib) is indicated:

- as a monotherapy for the first line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC).
- as a monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or who were intolerant to an ALK inhibitor (crizotinib).

(See 14 CLINICAL TRIALS)

1.1 Pediatrics

Pediatrics (< 18 years of age): No pediatric data have been made available to Health Canada; therefore, Health Canada has not approved an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Of the 359 patients treated with ALUNBRIG in the pivotal trials, 27% were 65 years of age and older. Increased age was associated with an increased risk of early pulmonary adverse reactions. There are limited data on the safety and efficacy of ALUNBRIG in patients aged 65 years and older. A dose adjustment is not required in elderly patients. There are no available data on patients over 85 years of age. (See 7 WARNINGS AND PRECAUTIONS, Respiratory.)

2 CONTRAINDICATIONS

ALUNBRIG (brigatinib) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Pulmonary Adverse Reactions (See 7 WARNINGS AND PRECAUTIONS, Respiratory)
- Hypertension (See 7 WARNINGS AND PRECAUTIONS, Cardiovascular)
- Elevation of pancreatic enzymes (See 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic)
- Hyperglycemia (See 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism)

- Creatine phosphokinase (CPK) elevation (See 7 WARNINGS AND PRECAUTIONS, Musculoskeletal)

ALUNBRIG should only be prescribed by a qualified healthcare professional who is experienced in the use of antineoplastic therapy.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

For patient monitoring and assessment prior to and during treatment with ALUNBRIG, see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests.

Geriatrics: No dose adjustment of ALUNBRIG is required in patients ≥ 65 years of age.

CYP3A Inhibitors: The concomitant use of ALUNBRIG with strong or moderate CYP3A inhibitors should be avoided. If concomitant use of strong or moderate CYP3A inhibitors cannot be avoided, the dose of ALUNBRIG should be reduced (See 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment; 7 WARNINGS AND PRECAUTIONS, General).

CYP3A Inducers: ALUNBRIG should not be administered with strong CYP3A inducers. The concomitant use of ALUNBRIG with moderate CYP3A inducers should be avoided. If concomitant use of moderate CYP3A inducers cannot be avoided, the dose of ALUNBRIG should be increased (See 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment; 7 WARNINGS AND PRECAUTIONS, General).

Hepatic Impairment: No dose adjustment of ALUNBRIG is required for patients with mild hepatic impairment (Child-Pugh class A) or moderate hepatic impairment (Child-Pugh class B). The dose of ALUNBRIG should be reduced for patients with severe hepatic impairment (Child-Pugh class C). (See 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment; 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations; 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions.)

Renal Impairment: No dose adjustment of ALUNBRIG is required for patients with mild or moderate renal impairment (creatinine clearance (CL_{cr}) ≥ 30 mL/min). The dose of ALUNBRIG should be reduced for patients with severe renal impairment (CL_{cr} < 30 mL/min). (See 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment; 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations; 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions.)

4.2 Recommended Dose and Dosage Adjustment

Standard Dose

The recommended dosing regimen for ALUNBRIG (brigatinib) is:

- 90 mg orally once daily for the first 7 days;
- If 90 mg is tolerated during the first 7 days, increase the dose to 180 mg orally once daily.

Duration of Treatment

Treatment with ALUNBRIG should be continued until disease progression or unacceptable toxicity.

Dose Modification Recommendations

Management of adverse events may require dosing interruption, dose reduction, or dose discontinuation of ALUNBRIG based on individual safety and tolerability.

Once reduced for adverse reactions, do not subsequently increase the dosage of ALUNBRIG. ALUNBRIG should be permanently discontinued if patient is unable to tolerate the 60 mg once daily dose.

If ALUNBRIG is interrupted for 14 days or longer for reasons other than adverse reactions, treatment should be resumed at 90 mg once daily for 7 days before increasing to the previously tolerated dose.

ALUNBRIG dose reduction levels for adverse reactions are summarized in **Table 1**.

Table 1 ALUNBRIG Dose Reduction Levels

Dose	**Dose Reduction Levels**		
	First	**Second**	**Third**
90 mg once daily (first 7 days)	60 mg once daily	Permanently discontinue	N/A*
180 mg once daily	120 mg once daily	90 mg once daily	60 mg once daily

*Not applicable

Recommendations for dose modifications of ALUNBRIG for the management of adverse reactions are summarized in **Table 2**.

Table 2 ALUNBRIG Dose Modifications for Specific Adverse Reactions

Adverse Reaction	Severity*	ALUNBRIG Dosing
Interstitial Lung Disease (ILD) /Pneumonitis	Grade 1	• If ILD/pneumonitis occurs during the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline, then resume at same dose and do not escalate to 180 mg if ILD/pneumonitis is suspected. • If ILD/pneumonitis occurs after the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline, then resume at same dose. • If ILD/pneumonitis recurs, permanently discontinue ALUNBRIG.
	Grade 2	• If ILD/pneumonitis occurs during the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline. Resume at next lower dose (**Table 1**) and do not dose escalate if ILD/pneumonitis is suspected. • If ILD/pneumonitis occurs after the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline. If ILD/pneumonitis is suspected, resume at next lower dose (**Table 1**); otherwise, resume at same dose. • If ILD/pneumonitis recurs, permanently discontinue ALUNBRIG.
	Grade 3 or 4	Permanently discontinue ALUNBRIG.
Hypertension	Grade 3 hypertension (SBP ≥ 160 mmHg or DBP ≥ 100 mmHg, medical intervention indicated, more than one anti-hypertensive drug, or more intensive therapy than previously used indicated)	• Withhold ALUNBRIG until hypertension has recovered to Grade ≤ 1 (SBP < 140 mmHg and DBP < 90 mmHg), or to baseline, then resume ALUNBRIG at same dose. • Recurrence: withhold ALUNBRIG until recovery to Grade ≤ 1, and resume at next lower dose (**Table 1**) or permanently discontinue treatment.

Adverse Reaction	Severity*	ALUNBRIG Dosing
	Grade 4 hypertension (life-threatening consequences, urgent intervention indicated)	• Withhold ALUNBRIG until recovery to Grade ≤1, and resume at next lower dose or permanently discontinue treatment (**Table 1**). • Recurrence: permanently discontinue ALUNBRIG for recurrence of Grade 4 hypertension.
Bradycardia (HR < 60 bpm)	Symptomatic bradycardia	• Withhold ALUNBRIG until recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. • If a concomitant medication known to cause bradycardia is identified and discontinued or dose-adjusted, resume ALUNBRIG at same dose upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above. • If no concomitant medication known to cause bradycardia is identified, or if contributing concomitant medications are not discontinued or dose-adjusted, resume ALUNBRIG at next lower dose (**Table 1**) upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above.
	Bradycardia with life-threatening consequences, urgent intervention indicated	• Permanently discontinue ALUNBRIG if no contributing concomitant medication is identified. • If contributing concomitant medication is identified and discontinued or dose-adjusted, resume ALUNBRIG at next lower dose (**Table 1**) upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. • Recurrence: permanently discontinue ALUNBRIG.
Visual Disturbance	Grade 2 or 3	Withhold ALUNBRIG until recovery to Grade 1 or baseline, then resume at the next lower dose (**Table 1**).
	Grade 4	Permanently discontinue ALUNBRIG.
Creatine Phosphokinase (CPK) Elevation	Grade 3 or 4 CPK elevation (>5.0 × ULN) with Grade ≥ 2 muscle pain or weakness	• Withhold ALUNBRIG until recovery to Grade ≤1 (≤ 2.5 × ULN) CPK elevation or to baseline, then resume ALUNBRIG at same dose. • Recurrence: Withhold ALUNBRIG until recovery to Grade ≤ 1 (≤ 2.5 × ULN) CPK elevation or to

Adverse Reaction	Severity*	ALUNBRIG Dosing
		baseline, then resume ALUNBRIG at next lower dose (**Table 1**).
Lipase/Amylase Elevation	Grade 3 lipase or amylase elevation (> 2.0 × ULN)	• Withhold ALUNBRIG until recovery to Grade ≤ 1 (≤ 1.5 × ULN) or to baseline, then resume ALUNBRIG at same dose. • Recurrence: Withhold ALUNBRIG until recovery to Grade 1 or less (≤ 1.5 × ULN) or to baseline, then resume ALUNBRIG at next lower dose (**Table 1**).
	Grade 4 lipase or amylase elevation (> 5.0 x ULN)	• Withhold ALUNBRIG until recovery to Grade ≤ 1 (≤ 1.5 × ULN) or to baseline, then resume ALUNBRIG at next lower dose (**Table 1**).
Hyperglycemia	Grade 3 (> 250 mg/dL or 13.9 mmol/L) or greater	If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved. Upon recovery, ALUNBRIG may either be resumed at the next lower dose (**Table 1**) or permanently discontinue ALUNBRIG.
Elevation of hepatic enzymes	Grade ≥ 3 elevation (>5.0 × ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with bilirubin ≤2 × ULN	ALUNBRIG should be withheld until recovery to baseline or less than or equal to 3 × ULN; then resume at next lower dose per **Table 1**.
	Grade ≥ 2 elevation (>3 × ULN) of ALT or AST with concurrent total bilirubin elevation >2 × ULN in the absence of cholestasis or haemolysis	ALUNBRIG should be permanently discontinued.
Other adverse reactions	Grade 3	• Withhold ALUNBRIG until recovery to baseline; then resume at same dose. • Recurrence: withhold ALUNBRIG until recovery to baseline; then resume at next lower dose or permanently discontinue ALUNBRIG (**Table 1**).

Adverse Reaction	Severity*	ALUNBRIG Dosing
	Grade 4	• Withhold ALUNBRIG until recovery to baseline and resume at next lower dose (**Table 1**). • Recurrence: Withhold ALUNBRIG until recovery to baseline and resume at next lower dose or permanently discontinue ALUNBRIG (**Table 1**).
bpm = beats per minute; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure; ULN = upper limit of normal		

*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4).

Strong or Moderate CYP3A Inhibitors: The concomitant use of ALUNBRIG with strong or moderate CYP3A inhibitors should be avoided. If concomitant use of strong CYP3A inhibitors cannot be avoided, the dose of ALUNBRIG should be reduced by approximately 50% (i.e., from 180 mg to 90 mg, or from 90 mg to 60 mg). If concomitant use of moderate CYP3A inhibitors cannot be avoided, the dose of ALUNBRIG should be reduced from 180 mg to 120 mg, 120 mg to 90 mg, or from 90 mg to 60 mg. After discontinuation of a strong or moderate CYP3A inhibitor, ALUNBRIG should be resumed at the dose that was tolerated prior to the initiation of the CYP3A inhibitor. (See 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions.)

Strong or Moderate CYP3A Inducers: ALUNBRIG should not be administered with strong CYP3A inducers. The concomitant use of ALUNBRIG with moderate CYP3A inducers should be avoided. If concomitant use of moderate CYP3A inducers cannot be avoided, the dose of ALUNBRIG should be increased in 30 mg increments after 7 days of treatment with the current ALUNBRIG dose as tolerated, up to a maximum of twice the ALUNBRIG dose that was tolerated prior to initiating the moderate CYP3A inducer. After discontinuation of a moderate CYP3A inducer, ALUNBRIG should be resumed at the dose that was tolerated prior to the initiation of the moderate CYP3A inducer. (See 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions.)

Special Populations

Pediatrics: No pediatric data have been made available to Health Canada; therefore, Health Canada has not approved an indication for pediatric use.

Geriatrics: No dose adjustment of ALUNBRIG is recommended for elderly patients based on population pharmacokinetic analyses. There are limited data on the safety and efficacy of ALUNBRIG in patients aged 65 years and older. There are no available data on patients over 85 years of age. (See 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions.)

Hepatic Impairment: No dose adjustment of ALUNBRIG is required for patients with mild hepatic impairment (Child-Pugh class A) or moderate hepatic impairment (Child-Pugh class B). The dose of ALUNBRIG should be reduced from 180 mg to 120 mg, 120 mg to 90 mg, or from 90 mg to 60 mg for patients with severe hepatic impairment (Child-Pugh class C). (See 7

WARNINGS AND PRECAUTIONS, 7.1 Special Populations; 10 CLINICAL PHARMACOLOGY, Special Populations and conditions.)

Renal Impairment: No dose adjustment of ALUNBRIG is required for patients with mild or moderate renal impairment (creatinine clearance (CL_{cr}) ≥ 30 mL/min). The dose of ALUNBRIG should be reduced by approximately 50% (e.g., from 180 mg to 90 mg, or from 90 mg to 60 mg) for patients with severe renal impairment (CL_{cr} < 30 mL/min). (See 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations; 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions.)

4.4 Administration

ALUNBRIG may be taken with or without food. The tablet should be swallowed whole with water. The tablet should not be crushed or chewed.

4.5 Missed Dose

If a dose of ALUNBRIG is missed or vomiting occurs after taking a dose, an additional dose should not be administered and the next dose of ALUNBRIG should be taken at the scheduled time.

5 OVERDOSAGE

There is no specific antidote for overdose with ALUNBRIG (brigatinib). In the event of an overdose, monitor the patient for adverse reactions and provide appropriate supportive care. (See 8 ADVERSE REACTIONS.)

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
oral	tablet 30 mg, 90 mg, and 180 mg	Lactose monohydrate, Magnesium stearate, Microcrystalline cellulose, Silica colloidal hydrophobic, Sodium starch glycolate (type A). The tablet coating consists of polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Packaging: ALUNBRIG (brigatinib) is supplied as follows:

- One-month initiation pack – Aclar/foil blister strip containing 7 of the 90 mg film-coated

tablets (1 card of 7 tablets) in a carton box and 21 of the 180 mg film-coated tablets (3 cards of 7 tablets) in a carton box, co-packaged in a single outer carton box
- 30 mg – Aclar/foil blister containing 28 film-coated tablets (2 cards of 14 tablets)
- 90 mg – Aclar/foil blister 28 film-coated tablets (4 cards of 7 tablets)
- 180 mg – Aclar/foil blister 28 film-coated tablets (4 cards of 7 tablets)

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Patients treated with ALUNBRIG (brigatinib) must have a documented ALK-positive status based on a validated ALK assay. Assessment for ALK-positive locally advanced or metastatic NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized.

Drug Interactions

The concomitant use of ALUNBRIG with strong or moderate CYP3A inhibitors should be avoided. If concomitant use of strong CYP3A inhibitors cannot be avoided, the dose of ALUNBRIG should be reduced by approximately 50% (i.e., from 180 mg to 90 mg, or from 90 mg to 60 mg). If concomitant use of moderate CYP3A inhibitors cannot be avoided, the dose of ALUNBRIG should be reduced from 180 mg to 120 mg, 120 mg to 90 mg, or from 90 mg to 60 mg. After discontinuation of a strong or moderate CYP3A inhibitor, ALUNBRIG should be resumed at the dose that was tolerated prior to the initiation of the CYP3A inhibitor. (See 9 DRUG INTERACTIONS.)

The concomitant use of ALUNBRIG with strong and moderate CYP3A inducers should be avoided. If concomitant use of moderate CYP3A inducers cannot be avoided, the dose of ALUNBRIG should be increased in 30 mg increments after 7 days of treatment with the current ALUNBRIG dose as tolerated, up to a maximum of twice the ALUNBRIG dose that was tolerated prior to the initiation of the moderate CYP3A inducer. After discontinuation of a moderate CYP3A inducer, ALUNBRIG should be resumed at the dose that was tolerated prior to the initiation of the moderate CYP3A inducer. (See 9 DRUG INTERACTIONS.)

Brigatinib is considered a weak inducer of CYP3A. Brigatinib may also induce other enzymes and transporters (e.g., CYP2C, P-gp) via the same mechanisms responsible for weak induction of CYP3A (e.g., pregnane X receptor activation). (See 9 DRUG INTERACTIONS.)

ALUNBRIG is not recommended for patients that are intolerant to lactose, as ALUNBRIG contains lactose.

Carcinogenesis and Mutagenesis

No carcinogenicity studies have been conducted with ALUNBRIG. *In vitro* and *in vivo* studies

demonstrated that brigatinib is aneugenic. (See 16 NON-CLINICAL TOXICOLOGY.)

Cardiovascular

Bradycardia

Bradycardia, sinus bradycardia, and prolongation of the PR interval has occurred in patients treated with ALUNBRIG in clinical trials. Caution should be exercised when administering ALUNBRIG in combination with other agents known to cause bradycardia. Heart rate and blood pressure should be monitored regularly. (See 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests; 8 ADVERSE REACTIONS; 10 CLINICAL PHARMACOLOGY, 10.2 Pharmacodynamics, Cardiac electrophysiology.)

In ALTA 1L (Phase 3), bradycardia was reported in 12% of patients treated with ALUNBRIG. Heart rates of less than 50 beats per minute (bpm) were reported in 8.1% of patients treated with ALUNBRIG at the recommended dose.

In ALTA (Phase 2), bradycardia was reported in 4.5% of patients treated with ALUNBRIG at the 180 mg regimen. Heart rates of less than 50 beats per minute (bpm) were reported in 8.2% of patients at the 180 mg regimen and 5.5% of patients at 90 mg regimen.

In a separate dose finding study, a decrease in heart rate was associated with increased ALUNBRIG plasma concentrations (C_{max}). (See 4 DOSAGE AND ADMINISTRATION; 8 ADVERSE REACTIONS.)

If symptomatic bradycardia occurs, treatment with ALUNBRIG should be withheld and concomitant medications known to cause bradycardia should be evaluated. Upon recovery, the dose should be modified accordingly. In case of life-threatening bradycardia, if no contributing concomitant medication is identified or in case of recurrence, treatment with ALUNBRIG should be discontinued (See **Table 2**). (See 4 DOSAGE AND ADMINISTRATION.)

Caution should be observed in patients with a low heart rate at baseline (< 60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, or congestive heart failure. Concomitant medications that result in a decrease in heart rate and/or PR interval prolongation should be avoided to the extent possible during treatment with ALUNBRIG. Advise patients to contact their healthcare provider to report these symptoms and to inform their healthcare provider about the use of any heart or blood pressure medications. (See 9 DRUG INTERACTIONS.)

Hypertension

In ALTA 1L, hypertension was reported in 32% of patients treated with ALUNBRIG; Grade 3 hypertension occurred in 13% of patients. (See 8 ADVERSE REACTIONS)

In ALTA, hypertension including Grade 3 hypertension as well as hypertensive retinopathy has occurred in 27% of patients treated with ALUNBRIG at the 180 mg regimen and 17% of patients at the 90 mg regimen. (See 8 ADVERSE REACTIONS; 8.2 Clinical Trial Adverse

Reactions, Additional Safety Information from Clinical Trial Experience for ALTA 1L and ALTA Studies.)

Blood pressure should be monitored regularly during treatment with ALUNBRIG. Hypertension should be treated according to standard guidelines to control blood pressure. Heart rate should be monitored more frequently in patients if concomitant use of a medicinal product known to cause bradycardia cannot be avoided. For severe hypertension (≥ Grade 3), ALUNBRIG should be withheld until hypertension has recovered to Grade 1 or to baseline. The dose should be modified accordingly. (See 4 DOSAGE AND ADMINISTRATION.)

Driving and Operating Machinery
Visual disturbances, dizziness, and fatigue have been observed in clinical trials in patients receiving ALUNBRIG. Patients should be advised not to drive or operate machines if they experience any of these symptoms.

Endocrine and Metabolism
Hyperglycemia
Elevations of serum glucose have occurred in patients treated with ALUNBRIG.
In ALTA 1L, 55% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 7.4% of patients.

In ALTA, 67% of patients experienced new or worsening hyperglycemia at 180 mg regimen and 46% of patients at 90m mg regimen. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 5.5% of patients at 180 mg regimen and 4.6% of the patients at 90 mg regimen. Three of 20 (15%) patients with diabetes or glucose intolerance at baseline required initiation of insulin while receiving ALUNBRIG.

Fasting serum glucose should be assessed prior to initiation of ALUNBRIG and monitored periodically thereafter, particularly in patients with diabetes. Antihyperglycemic medications should be initiated or optimized as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, ALUNBRIG should be withheld until adequate hyperglycemic control is achieved; upon recovery, reducing the dose of ALUNBRIG as described in **Table 1** may be considered or ALUNBRIG may be permanently discontinued (See **Table 2**). (See 4 DOSAGE AND ADMINISTRATION; 8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions, Additional Safety Information from Clinical Trial Experience for ALTA 1L and ALTA Studies.)

Hepatic/Biliary/Pancreatic
Elevations of pancreatic enzymes
Elevations of amylase and lipase have occurred in patients treated with ALUNBRIG.
In ALTA 1L, elevations of amylase and lipase were reported in 51% and 57% of patients treated with ALUNBRIG. Grade 3 and 4 incidences for amylase and lipase were 6.6% and 17%, respectively.

In ALTA, elevations of amylase were reported in 41% of patients treated with ALUNBRIG, at the 180 mg regimen and 31% of patients at the 90 mg regimen. Lipase elevations occurred in 46% of patients, at the 180 mg regimen and 30% of patients at the 90 mg regimen. Grade 3 and 4 incidences for amylase and lipase were 7.3% and 10%, respectively at the 180 mg regimen. Grade 3 and 4 incidences for amylase and lipase were 3.7% and 7.3%, respectively at the 90 mg regimen.

Lipase and amylase should be monitored regularly during treatment with ALUNBRIG. Based on the severity of the laboratory abnormalities, treatment with ALUNBRIG should be withheld, and the dose modified accordingly (See **Table 2**). (See 4 DOSAGE AND ADMINISTRATION; 8 ADVERSE REACTIONS; 8.2 Clinical Trial Adverse Reactions, Additional Safety Information from Clinical Trial Experience for ALTA 1L and ALTA Studies.)

Elevations of hepatic enzymes

Elevations of AST and ALT have occurred in patients treated with ALUNBRIG.
In ALTA 1L, elevations of ALT and AST occurred in 52% and 71% of patients treated with ALUNBRIG. Grade 3 and 4 incidences for ALT and AST were 5.1% and 4.4%, respectively.

In ALTA, elevations of ALT were reported in 45% of patients treated with ALUNBRIG, at the 180 mg regimen and 43% of patients at the 90 mg regimen. AST elevations were reported in 65% of patients treated with ALUNBRIG, at the 180 mg regimen and 50% of patients at the 90 mg regimen Grade 3 and 4 incidences for ALT and AST were 4.5 % and 2.7%, respectively at the 180 mg regimen. Grade 3 and 4 incidences for ALT and AST were 0.9% and 1.8%, respectively at the 90 mg regimen.

Hepatic function, including AST, ALT and total bilirubin should be assessed prior to the initiation of ALUNBRIG and then every 2 weeks during the first 3 months of treatment. Thereafter, monitoring should be performed periodically. Based on the severity of the laboratory abnormalities, treatment should be withheld, and the dose modified accordingly (See **Table 2**). (See 4 DOSAGE AND ADMINISTRATION; 8 ADVERSE REACTIONS; 8.2 Clinical Trial Adverse Reactions, Additional Safety Information from Clinical Trial Experience for ALTA 1L and ALTA Studies.)

Monitoring and Laboratory Tests

ALK Testing

Patients treated with ALUNBRIG must have a documented ALK-positive status based on a validated ALK assay. Assessment for ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized.

Cardiac Safety Monitoring

Heart rate and blood pressure should be monitored regularly during treatment with

ALUNBRIG. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with ALUNBRIG. Heart rate should be monitored more frequently in patients, if concomitant use with medications known to cause bradycardia cannot be avoided. (See 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 8 ADVERSE REACTIONS.)

Creatine Phosphokinase Monitoring

Patients should be advised to report any unexplained muscle pain, tenderness, or weakness. CPK levels should be monitored regularly during ALUNBRIG treatment. Based on the severity of the CPK elevation, treatment with ALUNBRIG should be withheld, and the dose modified accordingly (See **Table 2**). (See 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS, Musculoskeletal; 8 ADVERSE REACTIONS; 8.2 Clinical Trial Adverse Reactions, Additional Safety Information from Clinical Trial Experience for ALTA 1L and ALTA Studies.)

Pancreatic Enzyme Monitoring

Lipase and amylase should be monitored regularly during treatment with ALUNBRIG. (See 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; 8 ADVERSE REACTIONS; 8.2 Clinical Trial Adverse Reactions, Additional Safety Information from Clinical Trial Experience for ALTA 1L and ALTA Studies.)

Hepatic Enzyme Monitoring

Hepatic function, including AST, ALT and total bilirubin should be assessed prior to the initiation of ALUNBRIG and then every 2 weeks during the first 3 months of treatment. Thereafter, monitoring should be performed periodically. (See 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; 8 ADVERSE REACTIONS; 8.2 Clinical Trial Adverse Reactions, Additional Safety Information from Clinical Trial Experience for ALTA 1L and ALTA Studies.)

Glucose Monitoring

Fasting serum glucose should be assessed prior to initiation of ALUNBRIG and monitored periodically thereafter. Antihyperglycemic medications should be initiated or optimized as needed. (See 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS, Endocrine and metabolism; 8 ADVERSE REACTIONS.)

Musculoskeletal

Creatine phosphokinase (CPK) elevation

Elevations of CPK have occurred in patients treated with ALUNBRIG.

In ALTA 1L, elevations of CPK occurred in 75% of patients treated with ALUNBRIG, at the recommended dose. The incidence of Grade 3 or 4 elevations of CPK elevation was 22%.

In ALTA, elevations of CPK were reported in 50% of patients treated with ALUNBRIG, at the 180 mg regimen and 36% of patients at the 90 mg regimen. The incidence of Grade 3-4 elevation of CPK was 14% at the 180 mg regimen and 6.4% at the 90 mg regimen.

Patients should be advised to report any unexplained muscle pain, tenderness, or weakness. CPK levels should be monitored regularly during ALUNBRIG treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation with Grade 2 or higher muscle pain or weakness. Upon resolution or recovery to Grade 1 CPK elevation or baseline, resume ALUNBRIG at the same dose or at a reduced dose as described in **Table 1**. (See 4 DOSAGE AND ADMINISTRATION; 8 ADVERSE REACTIONS; 8.2 Clinical Trial Adverse Reactions, Additional Safety Information from Clinical Trial Experience for ALTA 1L and ALTA Studies.)

Ophthalmologic

Visual disturbance

Visual disturbance adverse reactions have occurred in patients treated with ALUNBRIG. Patients should be advised to report any visual symptoms.

In ALTA 1L, Grade 1 or 2 adverse reactions leading to visual disturbance including blurred vision, photophobia, photopsia, and reduced visual acuity were reported in 7.4% of patients receiving ALUNBRIG.

In ALTA, adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity, were reported in 16% of patients treated with ALUNBRIG at the 180 mg regimen and 8.3% of patients at the 90 mg regimen. Grade 3 macular edema and cataract occurred in 2 patients at the 180 mg regimen.

Withhold ALUNBRIG and obtain an ophthalmologic evaluation in patients with new or worsening visual symptoms of Grade 2 or greater severity. Upon recovery of Grade 2 or Grade 3 visual disturbances to Grade 1 severity or baseline, resume ALUNBRIG at a reduced dose (See **Table 2**). Permanently discontinue treatment with ALUNBRIG for Grade 4 visual disturbances. (See 4 DOSAGE AND ADMINISTRATION; 8 ADVERSE REACTIONS; 8.2 Clinical Trial Adverse Reactions, Additional Safety Information from Clinical Trial Experience for ALTA 1L and ALTA Studies.)

Reproductive Health: Female and Male Potential

Contraception in males and females

Women of child bearing age being treated with ALUNBRIG should be advised not to become pregnant and men being treated with ALUNBRIG should be advised not to father a child during treatment.

Women of reproductive potential should be advised to use effective non hormonal contraception during treatment with ALUNBRIG for at least 4 months following the final dose. Men with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG. (See 7 WARNING AND PRECAUTIONS, 7.1 Special Populations; 10 CLINICAL PHARMACOLOGY.)

- **Fertility**
  No human data on the effect of ALUNBRIG on fertility are available.
  Brigatinib may impair male fertility. Testicular toxicity was observed in repeat-dose animal studies. In rats, lower weight of testes, seminal vesicles and prostate gland, and testicular tubular degeneration; these effects were not reversible during the recovery period. In monkeys, reduced size of testes along with microscopic evidence of hypospermatogenesis were reported. These effects were reversible during the recovery period. Overall, these effects on the male reproductive organs in rats and monkeys occurred at exposures ≥0.2-times the AUC observed in patients at the 180 mg once daily dose. No apparent adverse effects on female reproductive organs were observed in general toxicology studies in rats and monkeys administered with brigatinib.

Respiratory

Pulmonary adverse reactions

Severe, life-threatening, and fatal pulmonary adverse reactions, including those with features consistent with Interstitial Lung Disease (ILD)/pneumonitis, were reported in patients treated with ALUNBRIG. (See 8 ADVERSE REACTIONS.)

In ALTA 1L (Phase 3), 5.1% of patients experienced ILD/pneumonitis, 2.9% of patients experienced any grade ILD/pneumonitis early in treatment (within 8 days), with Grade 3-4 ILD/pneumonitis in 2.2% of patients. Additionally, 3.7% of patients experienced pneumonitis later in treatment.

In ALTA (Phase 2), 6.4% of patients experienced pulmonary adverse reactions of any grade, including ILD/pneumonitis, pneumonia, and dyspnea, early in treatment (within 9 days, median onset: 2 days); 2.7% of patients had Grade 3-4 pulmonary adverse reactions and 1 patient (0.5%) had fatal pneumonia. Additionally, 2.3% of patients experienced pneumonitis following the second week of treatment, with 2 patients having Grade 3 pneumonitis. (See 4 DOSAGE AND ADMINISTRATION.)

In ALTA 1L and ALTA, most pulmonary adverse reactions (including dyspnea, hypoxia, cough, pneumonia and/or pneumonitis often with chest imaging of linear or ground-glass pulmonary opacities) were observed within the first 7 days of treatment initiation (or re-initiation, following a dose interruption), usually within 24-48 hours. The etiology of pulmonary adverse reactions is not known.
Grade 1-2 pulmonary adverse reactions resolved with interruption of treatment or dose modification. Increased age and shorter interval (less than 7 days) between the last dose of crizotinib and the first dose of ALUNBRIG were independently associated with an increased rate of these early pulmonary adverse reactions. These factors should be considered when initiating treatment with ALUNBRIG. (See 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations.) Patients with a history of ILD or drug-induced pneumonitis were excluded from ALTA.

Patients should be monitored for new or worsening respiratory symptoms (e.g., dyspnea,

cough, etc.), particularly in the first week of treatment. Evidence of pneumonitis in any patient with worsening respiratory symptoms should be promptly investigated. If pneumonitis is suspected, the dose of ALUNBRIG should be withheld, and the patient evaluated for other causes of symptoms (e.g., pulmonary embolism, tumour progression, and infectious pneumonia) and dose modified accordingly (See **Table 2**). (See 4 DOSAGE AND ADMINISTRATION.)

Skin

Photosensitivity

Photosensitivity to sunlight has been reported with ALUNBRIG (See 8 ADVERSE REACTIONS). Patients should be advised to avoid prolonged sun exposure while taking ALUNBRIG and for at least 5 days after discontinuation of treatment. Patients should also be advised to use a broad-spectrum Ultraviolet A (UVA)/Ultraviolet B (UVB) sun screen and lip balm (SPF at least 30) to help protect against potential sunburn. For severe photosensitivity reactions (≥ Grade 3), ALUNBRIG should be withheld until recovery to baseline. The dose should be modified accordingly (See **Table 2**). (See 4 DOSAGE AND ADMINISTRATION).

In ALTA1L, photosensitivity was reported in 3.7% of patients treated with ALUNBRIG, at the 180 mg regimen. Grade 3-4 photosensitivity occurred in 0.7% of patients.

In ALTA, photosensitivity was reported in 1.8% of patients treated with ALUNBRIG, at the 180 mg regimen and 1.8% of patients at the 90 mg regimen. Grade 3-4 photosensitivity occurred in 1 patient (0.9%) at the 180 mg regimen.

7.1 Special Populations

7.1.1 Pregnant Women

ALUNBRIG may cause fetal harm when administered to a pregnant woman. There are no clinical data on the use of ALUNBRIG in pregnant women. ALUNBRIG should not be used during pregnancy unless the clinical condition of the mother requires treatment. If ALUNBRIG is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. (See 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential.)

In an embryo-fetal development study in which pregnant rats were administered daily doses of brigatinib during organogenesis; dose-related skeletal anomalies were observed at doses as low as approximately 0.7-times the human exposure by AUC at the 180 mg once daily dose. Findings included embryo-lethality, reduced fetal growth, and skeletal variations.

7.1.2 Breast-feeding

It is not known whether brigatinib is excreted in human milk. Available data cannot exclude potential excretion of brigatinib in human milk. Because of the potential for adverse reactions

in breast feeding infants, advise lactating women not to breast feed during treatment with ALUNBRIG and for at least 1 week after the final dose.

7.1.3 Pediatrics

No pediatric data have been made available to Health Canada; therefore, Health Canada has not approved an indication for pediatric use.

7.1.4 Geriatrics

Pharmacokinetics of brigatinib in patients younger than 65 years of age was not significantly different from elderly patients based on population pharmacokinetic analyses. Of the 359 patients treated with ALUNBRIG in the pivotal trials, 27% were 65 years of age and older. Limited data on the safety and efficacy of ALUNBRIG in patients aged 65 years and older is available. There are no available data on patients over 85 years of age. Caution should be exercised when administering ALUNBRIG in elderly patients, especially in patients above 85 years of age. (See 7 WARNINGS AND PRECAUTIONS, Respiratory.)

7.1.5 Hepatic Impairment

No dose adjustment of ALUNBRIG is required for patients with mild hepatic impairment (Child-Pugh class A) or moderate hepatic impairment (Child-Pugh class B). The dose of ALUNBRIG should be reduced from 180 mg to 120 mg, 120 mg to 90 mg, or from 90 mg to 60 mg for patients with severe hepatic impairment (Child-Pugh class C). (See 4 DOSAGE AND ADMINISTRATION; 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions.)

7.1.6 Renal Impairment

No dose adjustment of ALUNBRIG is required for patients with mild or moderate renal impairment (creatinine clearance (CL_{cr}) ≥ 30 mL/min). The dose of ALUNBRIG should be reduced by approximately 50% (e.g., from 180 mg to 90 mg, or from 90 mg to 60 mg) for patients with severe renal impairment (CL_{cr} < 30 mL/min). (See 4 DOSAGE AND ADMINISTRATION; 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions.)

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Advanced ALK-positive NSCLC in TKI-naïve patients (ALTA 1L Study)

In ALTA 1L (Phase 3), a randomized, open-label, multicenter (ALTA 1L) trial, N = 275 patients with advanced ALK-positive NSCLC who had not previously received an ALK-targeted therapy were randomized in a 1:1 ratio to receive ALUNBRIG 180 mg once daily with a 7-day lead-in at 90 mg once daily (n=136) or crizotinib 250 mg orally twice daily (n=137).

The median duration of treatment was 24.3 months with 90 mg orally once daily with first 7 days; then increased to 180 mg orally once daily with ALUNBRIG. A total of 106 (78%) patients

were exposed to ALUNBRIG for greater than or equal to 6 months including 92 (68%) patients exposed for greater than or equal to 1 year. The median relative dose intensity was 97% for ALUNBRIG.

The most common adverse reactions reported in patients (≥10%) treated with ALUNBRIG were diarrhea, rash, cough, hypertension, fatigue, nausea, myalgia, dyspnea, abdominal pain, headache, vomiting, back pain, pruritis, constipation, edema, dizziness, arthralgia, stomatitis, blood cholesterol increased, bradycardia and peripheral neuropathy.

The most common Grade ≥ 3 adverse reactions reported in 5% or more of patients treated with ALUNBRIG were blood CPK increased (24%), lipase increased (14%), hypertension (13%), and amylase increased (5.9%).

The most common serious adverse reactions other than neoplasm progression reported in 2% or more of patients treated with ALUNBRIG included pneumonia (4.4%), ILD/pneumonitis (3.7%), pyrexia (2.9%), dyspnea (2.2%), pulmonary embolism (2.2%) and asthenia (2.2%).

Treatment-emergent adverse events (TEAEs) that led to discontinuation of ALUNBRIG occurred in 13% of patients. The most common TEAEs (occurring in ≥2 patients receiving ALUNBRIG) other than events related to neoplasm progression that led to ALUNBRIG discontinuation were ILD/pneumonitis 3.7% and pneumonia 2.2%.

TEAEs that led to dose reduction occurred in 38% of patients treated with ALUNBRIG. The TEAEs leading to dose reduction that occurred in ≥2% of patients receiving ALUNBRIG were blood CPK increased (15%), lipase increased (6.6%), amylase increased (4.4%, aspartate aminotransferase increased (2.2%), ILD/pneumonitis (2.2%) and hypertension (2.2%).

Advanced or metastatic ALK-positive NSCLC in previously crizotinib treated patients (ALTA Study)

In a randomized, Phase 2 open-label, multicenter (ALTA) ongoing trial, N = 219 patients with ALK-positive NSCLC who previously progressed on crizotinib were treated with ALUNBRIG (brigatinib). Patients were randomized in a 1:1 ratio to receive ALUNBRIG either 90 mg once daily continuously (90 mg regimen) or 180 mg once daily with 7-day lead-in at 90 mg once daily (180 mg regimen). Dose reduction to 60 mg was possible in both arms in case of adverse events.

The median duration of treatment with ALUNBRIG was 15.4 months in all treated patients (13.2 months and 17.1 months in 90 mg regimen and 180 mg regimen, respectively).

The most common adverse reactions reported in patients (≥10%) treated with ALUNBRIG at the 180 mg recommended regimen were nausea, diarrhea, fatigue, cough, headache, rash, vomiting, hypertension, dyspnea, myalgia, decreased appetite, muscle spasms, constipation, peripheral neuropathy, arthralgia, visual disturbances, abdominal pain, dizziness, edema and ILD/pneumonitis.

The most common Grade ≥ 3 adverse reactions other than neoplasm progression reported in 5% or more of patients treated with ALUNBRIG at 180 mg recommended regimen were blood CPK increased (13%), hypertension (8.2%) and pneumonia (5.5%).

The most common serious adverse reactions other than neoplasm progression or malignant pleural effusion reported in 2% or more of patients in the 180 mg regimen included pneumonia (8.2%) and pneumonitis (8.2%).

Treatment emergent adverse events (TEAEs) that led to discontinuation of ALUNBRIG occurred in 11% (12/110) of patients receiving the 180 mg regimen. The most common TEAEs (occurring in ≥2 patients receiving the 180 mg regimen) that led to ALUNBRIG discontinuation were pneumonitis, neoplasm progression, and pneumonia (2.7% [3/110], 1.8% [2/110], and 1.8% [2/110], respectively).

TEAEs that led to dose reduction occurred in 30% (33/110) of patients receiving the 180 mg regimen. The TEAEs leading to dose reduction that occurred in ≥2% of patients receiving the 180 mg regimen were blood CPK increased (6.4% (7/110), pneumonitis (2.7% [3/110]), and rash (2.7% [3/110]).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Advanced ALK-positive NSCLC in TKI-naïve patients (ALTA 1L Study, Phase 3)

Table 4 Adverse Reactions Occurring in ≥2% (All Grades)* of Patients treated with ALUNBRIG versus crizotinib in ALTA 1L (N=273)

Adverse Reactions	ALUNBRIG		Crizotinib	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Cardiac Disorders				
Bradycardia¶	16 (12)	1 (0.7)	32 (23)	0
Electrocardiogram QT prolonged	7 (5.1)	2 (1.5)	8 (5.8)	0
Eye Disorders				
Visual Disturbance§	10 (7.4)	0	72 (53)	1 (0.7)
Gastrointestinal Disorders				
Diarrhea	71 (52)	3 (2.2)	77 (56)	4 (2.9)
Nausea	41 (30)	3 (2.2)	80 (58)	4 (2.9)
Abdominal Pain**	33 (24)	1 (0.7)	45 (33)	5 (3.6)
Vomiting	28 (21)	1 (0.7)	60 (44)	3 (2.2)
Constipation	25 (18)	0	57 (42)	0
Stomatitis‡‡‡	18 (13)	1 (0.7)	12 (8.8)	0
Dyspepsia	11 (8)	0	22 (16)	1 (0.7)
Dry mouth	7 (5.1)	0	5 (3.6)	0
Gastroesophageal Reflux Disease	1 (0.7)	0	15 (11)	0
General Disorders and Administration Site Conditions				
Fatigue§§	43 (32)	2 (1.5)	55 (40)	3 (2.2)
Edema¶¶	25 (18)	1 (0.7)	66 (48)	1 (0.7)
Malaise	6 (4.4)	0	3 (2.2)	0
Mucosal Inflammation	5 (3.7)	1 (0.7)	3 (2.2)	0
Hepatobiliary Disorders				
Blood lactate dehydrogenase	6 (4.4)	0	5 (3.6)	0
Gamma glutamyl transferase	3 (2.2)	2 (1.5)	8 (5.8)	3 (2.2)
Investigations				
Blood cholesterol Increased ᵖᵖ	17 (13)	0	1 (0.7)	0
Weight increased	2 (1.5)	0	3 (2.2)	0
Metabolism and Nutrition Disorders				
Decreased Appetite	12 (8.8)	1 (0.7)	26 (19)	4 (2.9)
Dyslipidemia	4 (2.9)	0	0	0

Adverse Reactions	ALUNBRIG		Crizotinib	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Musculoskeletal and Connective Tissue Disorders				
Myalgia‡‡	38 (28)	0	32 (23)	0
Back pain	29 (21)	1 (0.7)	23 (17)	2 (1.5)
Arthralgia	19 (14)	0	17 (12)	0
Pain in extremity	7 (5.1)	0	20 (15)	1 (0.7)
Nervous System Disorders				
Headache†	30 (22)	3 (2.2)	23 (17)	0
Dizziness	20 (15)	1 (0.7)	28 (20)	1 (0.7)
Peripheral Neuropathy‡	15 (11)	1 (0.7)	25 (18)	0
Dysgeusia	4 (2.9)	0	19 (14)	0
Taste disorder	2 (1.5)	0	8 (5.8)	0
Psychiatric Disorders				
Insomnia	11 (8.1)	0	12 (8.8)	0
Depression	4 (2.9)	0	8 (5.8)	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	47 (35)	0	27 (20)	0
Dyspnea Þ, ė	34 (25)	4 (2.9)	30 (22)	5 (3.6)
Productive cough	12 (8.8)	0	11 (8)	0
Dysphonia	8 (5.9)	0	6 (4.4)	0
Interstitial Lung Disease (ILD)/Pneumonitis	7 (5.1)	4 (2.9)	3 (2.2)	1 (0.7)
Skin and Subcutaneous Tissue Disorders				
Rash††	54 (40)	4 (2.9)	23 (17)	0
Pruritis†††	27 (20)	1 (0.7)	8 (5.8)	1 (0.7)
Dry Skin	7 (5.1)	0	6 (4.4)	0
Photosensitivity reaction	5 (3.7)	1 (0.7)	1 (0.7)	0
Acne	4 (2.9)	0	1 (0.7)	0
Rash generalized	4 (2.9)	0	0	0
Vascular Disorders				
Hypertension***	44 (32)	17 (13)	11 (8)	4 (2.9)
Hypotension	1 (0.7)	0	10 (7.3)	0

Adverse Reactions	ALUNBRIG		Crizotinib	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)

* Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, includes ADRs that were treatment-related percentage in ≥2% of patients in either arm. Actual number and percentages presented are based on the treatment-emergent adverse events.
¶ Includes bradycardia, heart rate decreased, sinus bradycardia
§ Includes cataract, diplopia, glaucoma, hypermetropia, night blindness, papilledema, photophobia, photopsia, blurred vision, reduced visual acuity, visual field defect, visual impairment, vitreous floaters
** Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort
‡‡‡ Includes aphthous ulcer, mouth ulceration, oral mucosal blistering, stomatitis
§§ Includes asthenia, fatigue
¶¶Includes angioedema, eye swelling, eyelid oedema, face oedema, generalised oedema, lip swelling, peripheral oedema, periorbital oedema, periorbital swelling, peripheral swelling, skin swelling, swelling, swelling face, swelling of eyelid
‡‡ Includes muscle spasms, muscle twitching, musculoskeletal discomfort, musculoskeletal pain, myalgia
† Includes headache and migraine
‡ Includes burning sensation, dysesthesia, hyperesthesia, hypoesthesia, neuralgia, peripheral neuropathy, paresthesia, peripheral sensory neuropathy, polyneuropathy
Þ Includes dyspnea, dyspnea exertional
††Includes dermatitis, dermatitis acneiform, dermatitis bullous, dermatitis contact, drug eruption, erythema, generalised erythema, palmar-plant erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic skin eruption, urticaria
††† Includes ear pruritis, eye pruritis, pruritis, pruritis allergic, pruritis generalised, pruritis genital
ÞÞ Includes blood cholesterol increased and hypercholesterolaemia
*** Includes diastolic hypertension, hypertension, systolic hypertension
è Includes Grade 5 events

Additional Safety Information from Clinical Trial Experience (ALTA 1L)

Visual Disturbance

In ALTA 1L (Phase 3), visual disturbance adverse reactions were reported in 7.4% of patients receiving ALUNBRIG at the recommended dose. There were no Grade 3 visual disturbance events. There were no dose reductions due to visual disturbance (any grade). (See 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS.)

Creatine Phosphokinase (CPK) Elevation

In ALTA 1L, elevations of creatine phosphokinase (CPK) occurred in 75% of patients treated with ALUNBRIG at the recommended dose. The incidence of Grade 3 or 4 elevations of CPK elevation was 22%.

Dose reduction for CPK elevation occurred in 15% of patients. (See 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS.)

Elevations of Pancreatic Enzymes

In ALTA 1L, elevations of amylase and lipase were reported in 51% and 57% of patients treated with ALUNBRIG. For elevations to Grade 3 and 4, the incidences for amylase and lipase were 6.6% and 17%, respectively.

Dose reduction for elevation of amylase and lipase occurred in 4.4% and 6.6% of patients, respectively, receiving ALUNBRIG. (See 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS.)

Elevations of Hepatic Enzymes

In ALTA 1L, elevations of ALT and AST occurred in 52% and 71% of patients treated with ALUNBRIG. For elevations to Grade 3 and 4, the incidences for ALT and AST were 5.1% and 4.4%, respectively.

Hyperglycemia and Elevations of Insulin

In ALTA 1L, 55% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia occurred in 7.4% of patients and 40% of patients experienced elevations of insulin.

Photosensitivity

In ALTA 1L, photosensitivity was reported in 3.7% of patients treated with ALUNBRIG, at the 180 mg regimen. Grade 3-4 photosensitivity occurred in 0.7% of patients.

Advanced or metastatic ALK-positive NSCLC in previously crizotinib treated patients (ALTA Study, Phase 2)

Table 5 Adverse Reactions Occurring in ≥2% (All Grades)* of Patients treated with ALUNBRIG by Dosing Regimen (90 mg Once Daily and 90 →180 mg Once Daily) in ALTA

Adverse Reactions	90 mg once daily N = 109		90→180 mg once daily N = 110	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Cardiac Disorders				
Bradycardia[¶]	7 (6.4)	0	5 (4.5)	0
Electrocardiogram QT prolonged	3 (2.8)	1 (0.9)	7 (6.4)	1 (0.9)
Palpitations	1 (0.9)	0	5 (4.5)	0
Eye Disorders				
Visual Disturbance[§]	9 (8.3)	0	18 (16)	2 (1.8)
Gastrointestinal Disorders				
Nausea	41 (38)	1 (0.9)	52 (47)	1 (0.9)
Diarrhea	30 (28)	1 (0.9)	48 (44)	0
Vomiting	39 (36)	2 (1.8)	33 (30)	0
Constipation	24 (22)	1 (0.9)	22 (20)	0
Abdominal Pain[Þ]	22 (20)	1 (0.9)	16 (15)	2 (1.8)
Dry mouth	4 (3.7)	0	10 (9.1)	0
Stomatitis	4 (3.7)	1 (0.9)	9 (8.2)	0
Dyspepsia	7 (6.4)	0	7 (6.4)	1 (0.9)
General Disorders and Administration Site Conditions				
Fatigue[¶¶]	41 (38)	3 (2.8)	46 (42)	1 (0.9)
Pyrexia	21 (19)	0	9 (8.2)	1 (0.9)
Edema[##]	12 (11)	0	12 (11)	0
Non-cardiac chest pain	7 (6.4)	1 (0.9)	4 (3.6)	1 (0.9)
Metabolism and Nutrition Disorders				
Decreased appetite	28 (26)	1 (0.9)	26 (24)	1 (0.9)
Musculoskeletal and Connective Tissue Disorders				
Myalgia[‡‡]	13 (12)	0	27 (25)	1 (0.9)
Muscle Spasms	16 (15)	0	24 (22)	0
Arthralgia	18 (17)	1 (0.9)	18 (16)	0
Musculoskeletal chest pain	7 (6.4)	1 (0.9)	9 (8.2)	0
Pain in extremity	16 (15)	1 (0.9)	9 (8.2)	2 (1.8)
Increased creatine phosphokinase[§§]	39 (36)	7 (6.4)	55 (50)	15 (14)

Adverse Reactions	90 mg once daily N = 109		90→180 mg once daily N = 110	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Nervous System Disorders				
Headache[†]	33 (30)	0	39 (35)	2 (1.8)
Peripheral Neuropathy[‡]	17 (16)	1 (0.9)	20 (18)	3 (2.7)
Dizziness	15 (14)	0	16 (15)	0
Dysgeusia	5 (4.6)	0	6 (5.5)	0
Psychiatric Disorders				
Insomnia	18 (17)	0	10 (9.1)	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	31 (28)	0	44 (40)	0
Dyspnea[#]	33 (30)	3 (2.8)	29 (26)	2 (1.8)
Interstitial Lung Disease(ILD)/Pneumonitis	5 (4.6)	3 (2.8)	11 (10)	4 (3.6)
Skin and Subcutaneous Tissue Disorders				
Rash**	20 (18)	2 (1.8)	35 (32)	5 (4.5)
Pruritus	9 (8.3)	0	11 (10)	0
Dry skin	7 (6.4)	0	2 (1.8)	0
Photosensitivity[††]	2 (1.8)	0	2 (1.8)	1 (0.9)
Vascular Disorders				
Hypertension	19 (17)	6 (5.5)	30 (27)	9 (8.2)

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, includes ADRs that were treatment-related percentage in ≥2% of patients in either arm. Actual number and percentages presented are based on the treatment-emergent adverse events.

[¶] Includes bradycardia and sinus bradycardia

[§]Includes cataract, diplopia, glaucoma, macular edema, photophobia, photopsia, retinal edema, vision blurred, visual acuity reduced, visual field defect, visual impairment, vitreous detachment, and vitreous floaters

[Þ]Includes abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort

[¶¶]Includes asthenia and fatigue

[##]Includes face edema, edema peripheral, periorbital edema, and swelling face

[‡‡]Includes musculoskeletal pain and myalgia

[§§] Based on laboratory assessment

[†]Includes headache and sinus headache

[‡]Includes peripheral sensory neuropathy and paresthesia

[#]Includes dyspnea and exertional dyspnea

**Includes dermatitis acneiform, erythema, exfoliative rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular

[††]Photosensitivity did not meet the threshold of >2% (all grades) but is considered an Adverse Drug Reactions (ADR)

Additional Safety Information from Clinical Trial Experience (ALTA)

Pulmonary Adverse Reactions

In ALTA (Phase 2), 6.4% of patients experienced pulmonary adverse reactions of any grade, including ILD/pneumonitis, pneumonia, and dyspnea, early in treatment (within 9 days, median onset: 2 days); 2.7% of patients had Grade 3-4 pulmonary adverse reactions and 1 patient (0.5%) had fatal pneumonia. Following Grade 1-2 pulmonary adverse reactions, treatment with ALUNBRIG was either interrupted and then restarted or the dose was reduced.

Additionally, 2.3% of patients experienced pneumonitis later in treatment (median onset: 150 days), with 2 patients having Grade 3 pneumonitis. (See 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS.)

In ALTA, 13% of patients ≥ 65 years of age experienced an early pulmonary adverse reaction compared with 4.2% of patients with <65 years of age.

Hypertension

In ALTA, hypertension was reported in 27% of patients treated with ALUNBRIG at the 180 mg regimen with 8.2% having Grade 3 hypertension. Dose reduction for hypertension occurred in 0.9% at the 180 mg regimen. Systolic and diastolic blood pressure increased over time. (See 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS.)

Bradycardia

In ALTA, bradycardia was reported in 4.5% of patients treated with ALUNBRIG at the 180 mg regimen.

Heart rates of less than 50 beats per minute (bpm) were reported in 8.2% of patients at the 180 mg regimen and 5.5% of patients at 90 mg regimen. In a separate dose finding study (Study 101), a decrease in heart rate was associated with increased ALUNBRIG plasma concentrations (C_{max}). (See 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS.)

In the dose finding study, a concentration-dependent prolongation of the PR interval was observed with the use of ALUNBRIG; however, the mean absolute values of the PR interval for 180 mg dose remained within 120-200 milliseconds. (See 8 ADVERSE REACTIONS.)

Visual Disturbance

In ALTA, visual disturbance adverse reactions were reported in 16% of patients treated with brigatinib at the 180 mg regimen. Of these, two Grade 3 adverse reactions (1.8%), including macular edema and cataract, were reported.

Dose reduction for visual disturbance occurred in two patients (1.8%) at the 180 mg regimen. (See 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS.)

Creatine Phosphokinase (CPK) Elevation

In ALTA, elevations of creatine phosphokinase (CPK) were reported in 50% of patients treated with ALUNBRIG at the 180 mg regimen. The incidence of Grade 3-4 elevations of CPK was 14%. The median time to onset for CPK elevations was 27 days.

Dose reduction for CPK elevation occurred in 6.4% patients at the 180 mg regimen. (See 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS.)

Elevations of Pancreatic Enzymes

In ALTA, elevations of amylase and lipase were reported in 41% and 46% of patients treated with ALUNBRIG, respectively at the 180 mg regimen. For elevations to Grade 3 and 4, the incidences for amylase and lipase were 7.3% and 10%, respectively. The median time to onset for amylase elevations and lipase elevations was 16 days and 29 days, respectively.

Dose reduction for elevation of lipase and amylase occurred in 1.8% and 0.9% of patients, respectively, at the 180 mg regimen. (See 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS.)

Elevations of Hepatic Enzymes

In ALTA, elevations of ALT and AST were reported in 45% and 65% of patients treated with ALUNBRIG, respectively, at the 180 mg regimen. For elevations to Grade 3 and 4, the incidences for ALT and AST were 4.5% and 2.7%, respectively.

Hyperglycemia and Elevations of Insulin

In ALTA, 67% of patients experienced hyperglycemia. Grade 3 hyperglycemia occurred in 5.5% of patients and 59% of patients experienced elevations of insulin.

Photosensitivity

In ALTA, photosensitivity was reported in 1.8% of patients treated with ALUNBRIG, at the 180 mg regimen and 1.8% of patients at the 90 mg regimen. Grade 3-4 photosensitivity occurred in 1 patient (0.9%) at the 180 mg regimen.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Table 6 and **Table 7** display laboratory abnormalities occurring in patients in the ALTA 1L (Phase 3) and ALTA (Phase 2) Clinical Trials.

Advanced ALK-positive NSCLC in TKI-naïve patients (ALTA 1L Study)

Table 6 Laboratory Abnormalities Occurring in ≥20% (All Grades)* of Patients treated with ALUNBRIG versus crizotinib in ALTA 1L (N = 273)

Laboratory Abnormality	ALUNBRIG N = 136		Crizotinib N = 137	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Chemistry				
Increased creatine phosphokinase	102 (75)	30 (22)	85 (62)	6 (4.4)
Increased aspartate aminotransferase	96 (71)	6 (4.4)	94 (69)	7 (5.1)
Increased lipase	78 (57)	23 (17)	48 (35)	13 (9.5)
Hyperglycemia†	75 (55)	10 (7.4)	50 (37)	5 (3.6)
Increased alanine aminotransferase	70 (52)	7 (5.1)	103 (75)	17 (12)
Increased amylase	69 (51)	9 (6.6)	33 (24)	4 (2.9)
Decreased phosphorous	55 (40)	5 (3.7)	52 (38)	8 (5.8)
Increased alkaline phosphatase	48 (35)	4 (2.9)	65 (47)	2 (1.5)
Increased creatinine	33 (24)	0	45 (33)	0
Potassium increased	32 (24)	2 (1.5)	42 (31)	5 (3.6)
Increased calcium	29 (21)	0	2 (1.5)	0
Decreased magnesium	28 (21)	0	9 (6.6)	0
Decreased albumin	19 (14)	1 (0.7)	69 (50)	5 (3.6)
Decreased calcium	19 (14)	0	88 (64)	2 (1.5)
Hematology				
Hemoglobin decreased	54 (40)	3 (2.2)	49 (36)	2 (1.5)
Lymphocyte count decreased	36 (27)	8 (5.9)	28 (20)	5 (3.6)
Neutrophil count decreased	10 (7.4)	0	30 (22)	6 (4.4)

* Per CTCAE version 4.0

† Elevated blood insulin was also observed in both regimens

Advanced or metastatic ALK-positive NSCLC in previously crizotinib treated patients (ALTA Study)

Table 7 Laboratory Abnormalities Occurring in ≥20% (All Grades)* of Patients treated with ALUNBRIG by Dosing Regimen in ALTA

Laboratory Abnormality	90 mg once daily N= 109		90→180 mg once daily N=110	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Chemistry				
Blood creatinine increased‡	12 (11)	0	16 (15)	0
Hyperglycemia†	50 (46)	5 (4.6)	74 (67)	6 (5.5)
Increased aspartate aminotransferase	55 (50)	2 (1.8)	71 (65)	3 (2.7)
Increased lipase	33 (30)	8 (7.3)	51 (46)	11 (10)
Increased alanine aminotransferase	47 (43)	1 (0.9)	50 (45)	5 (4.5)
Increased amylase	34 (31)	4 (3.7)	45 (41)	8 (7.3)
Increased alkaline phosphatase	24 (22)	3 (2.8)	43 (39)	3 (2.7)
Decreased phosphorous	28 (26)	4(3.7)	35 (32)	7 (6.4)
Prolonged activated partial thromboplastin time	36 (33)	2 (1.8)	31 (28)	1 (0.9)
Decreased potassium	13 (12)	2 (1.8)	24 (22)	2 (1.8)
Decreased magnesium	22 (20)	0	22 (20)	0
Decreased sodium	28 (26)	8 (7.3)	22 (20)	4 (3.6)
Hematology				
Anemia	36 (33)	1 (0.9)	54 (49)	2 (1.8)
Decreased white blood cell count	20 (18)	0	26 (24)	0
Lymphopenia	33 (30)	5 (4.6)	44 (40)	14 (13)

*Per CTCAE version 4.0

†Elevated blood insulin was also observed in both regimens

‡Blood creatinine increase did not meet the threshold of >20% (all grades) but is considered as an ADR

Other Adverse Reactions from Multiple Clinical Trials

In a pooled clinical trial population consisting of three studies with 274 patients treated with ALUNBRIG at the recommended dose, the following adverse events and laboratory abnormalities were reported: upper respiratory tract infection (12%), decreased platelet count (9.9%), pain (3.3%) and musculoskeletal stiffness (1.1%).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

In vitro studies demonstrated that brigatinib is primarily metabolized by CYP2C8 and CYP3A4. *In vitro* studies in hepatocytes have shown that brigatinib is an inducer of CYP3A. Brigatinib is an inhibitor of P-gp, BCRP, OCT1, MATE1, and MATE2K *in vitro*.

9.3 Drug-Behavioural Interactions

There are no data on the effect of ALUNBRIG on the ability to drive and use machines. Visual disturbances, dizziness, and fatigue have been observed in clinical trials. Patients should be advised not to drive or operate machines if they experience any of these symptoms while taking ALUNBRIG.

9.4 Drug-Drug Interactions

Agents that may increase brigatinib plasma concentrations

Strong and Moderate CYP3A Inhibitors
In vitro studies demonstrated that brigatinib is a substrate of CYP3A4/5. Coadministration of multiple 200 mg twice daily doses of itraconazole, a strong CYP3A inhibitor, with a single 90 mg brigatinib dose increased brigatinib C_{max} by 21% and $AUC_{0\text{-}INF}$ by 101% (2-fold), relative to a 90 mg brigatinib dose administered alone (See **Table 8**).

Moderate CYP3A inhibitors (e.g., diltiazem and verapamil) are predicted to increase the AUC of brigatinib by approximately 40% based on simulations from a physiologically-based pharmacokinetic (PBPK) model (See **Table 8**).

Grapefruit or grapefruit juice may also increase plasma concentrations of brigatinib and should be avoided.

CYP2C8 Inhibitors
In vitro studies demonstrated that brigatinib is a substrate of CYP2C8. Coadministration of multiple 600 mg twice daily doses of gemfibrozil, a strong CYP2C8 inhibitor, with a single 90 mg brigatinib dose decreased brigatinib C_{max} by 41% and $AUC_{0\text{-}INF}$ by 12%, relative to a 90 mg brigatinib dose administered alone. No dose adjustment is required for ALUNBRIG during coadministration with strong CYP2C8 inhibitors.

P-gp and BCRP Inhibitors
Brigatinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) *in vitro*. Brigatinib exhibits high solubility and high permeability. Therefore, inhibition of P-gp and BCRP is not expected to result in a clinically meaningful change in the systemic exposure of brigatinib. No dose adjustment is required for ALUNBRIG during coadministration with P-gp and BCRP inhibitors.

Agents that may decrease brigatinib plasma concentrations

Strong and Moderate CYP3A Inducers
In vitro studies demonstrated that brigatinib is a substrate of CYP3A4/5. Coadministration of multiple 600 mg daily doses of rifampin, a strong CYP3A inducer, with a single 180 mg brigatinib dose decreased brigatinib C_{max} by 60% and $AUC_{0\text{-}INF}$ by 80% (5-fold), relative to a 180 mg brigatinib dose administered alone (See **Table 8**).

Moderate CYP3A inducers are predicted to decrease the AUC of brigatinib by approximately 50% based on simulations from a physiologically-based pharmacokinetic model (See **Table 8**).

Agents that may have their plasma concentrations altered by brigatinib

CYP3A Substrates
In vitro studies in hepatocytes have shown that brigatinib is an inducer of CYP3A. Coadministration of multiple 180 mg daily doses of ALUNBRIG with a single 3 mg oral dose of midazolam, a sensitive CYP3A substrate, decreased midazolam C_{max} by 16%, $AUC_{0\text{-}INF}$ by 26% and $AUC_{0\text{-}last}$ by 30%, relative to a 3 mg oral dose of midazolam administered alone. Brigatinib is considered a weak inducer of CYP3A (See **Table 8**).

Transporter Substrates
Brigatinib is an inhibitor of P-gp, BCRP, OCT1, MATE1, and MATE2K *in vitro*. Coadministration of brigatinib with substrates of P-gp, BCRP, OCT1, MATE1, and MATE2K may increase their plasma concentrations (See **Table 8**).

Agents that decrease heart rate

ALUNBRIG results in a decrease in heart rate and an increase in the PR interval. The concomitant use of ALUNBRIG with other drugs that lower heart rate and/or prolong the PR interval should be avoided to the extent possible. (See **Table 8**; 7 WARNINGS AND PRECAUTIONS, Cardiovascular & Monitoring and Laboratory Tests; 10 CLINICAL PHARMACOLOGY, Cardiac Electrophysiology.)

Table 8 Established or Potential Drug-Drug Interactions with ALUNBRIG

Common name	Source of Evidence	Effect	Clinical comment
Pharmacokinetic Interactions (Drugs that may affect the exposure to brigatinib)			
Strong CYP3A inhibitors (e.g., itraconazole, clarithromycin, telithromycin, ritonavir, cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir)	CT	Increased brigatinib C_{max} by 21% and AUC_{0-INF} by 101%.	The concomitant use of strong CYP3A inhibitors with ALUNBRIG should be avoided. If concomitant use of strong CYP3A inhibitors cannot be avoided, the dose of ALUNBRIG should be reduced by approximately 50% (i.e.., from 180 mg to 90 mg, or from 90 mg to 60 mg). After discontinuation of a strong CYP3A inhibitor, ALUNBRIG should be resumed at the dose that was tolerated prior to the initiation of the strong CYP3A inhibitor.
Strong CYP3A inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's Wort)	CT	Decreased brigatinib C_{max} by 60% and AUC_{0-INF} by 80% (5-fold).	ALUNBRIG should not be administered with strong CYP3A inducers.
Moderate CYP3A inhibitors (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil)	CT	Moderate CYP3A inhibitors are predicted to increase the AUC of brigatinib by approximately 40% based on simulations from a physiologically-based pharmacokinetic (PBPK) model.	The concomitant use of moderate CYP3A inhibitors with ALUNBRIG should be avoided. If concomitant use of moderate CYP3A inhibitors cannot be avoided, the dose of ALUNBRIG should be reduced from 180 mg to 120 mg, 120 mg to 90 mg, or from 90 mg to 60 mg. After discontinuation of a moderate CYP3A inhibitor, ALUNBRIG should be resumed at the dose that was tolerated prior to the initiation of the moderate CYP3A inhibitor.

Common name	Source of Evidence	Effect	Clinical comment
Moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin)	CT	Moderate CYP3A inducers are predicted to decrease the AUC of brigatinib by approximately 50% based on simulations from a PBPK model.	The concomitant use of moderate CYP3A inducers with ALUNBRIG should be avoided. If concomitant use of moderate CYP3A inducers cannot be avoided, the dose of ALUNBRIG should be increased in 30 mg increments after 7 days of treatment with the current ALUNBRIG dose as tolerated, up to a maximum of twice the ALUNBRIG dose that was tolerated prior to initiating the moderate CYP3A inducer. After discontinuation of a moderate CYP3A inducer, ALUNBRIG should be resumed at the dose that was tolerated prior to the initiation of the moderate CYP3A inducer.
Pharmacokinetic Interactions (Drugs for which the exposure may be affected by brigatinib)			
Sensitive substrates of CYP3A (e.g., simvastatin, cyclosporine, cisapride, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus, quetiapine)	CT	Brigatinib decreased the C_{max}, $AUC_{0\text{-}INF}$ and $AUC_{0\text{-}last}$ of midazolam, a sensitive CYP3A substrate, by 16%, 26% and 30% respectively.	Brigatinib may decrease concentrations of CYP3A substrates. Patients receiving CYP3A substrates with a narrow therapeutic index should be closely monitored for loss of efficacy during coadministration with ALUNBRIG
Substrates of pregnane X receptor (PXR) inducible enzymes and transporters (e.g., CYP2C, P-gp)	T	The effect of brigatinib on the pharmacokinetics of substrates of PXR inducible enzymes and transporters has not been studied.	Brigatinib may also induce other enzymes and transporters and decrease concentrations of their substrates via the same mechanisms responsible for weak induction of CYP3A (e.g., pregnane X receptor activation). Patients receiving these substrates with a narrow therapeutic index should be closely monitored for loss of efficacy during coadministration with ALUNBRIG

Common name	Source of Evidence	Effect	Clinical comment
Substrates of P-gp, BCRP, OCT1, MATE1, and MATE2K (e.g., digoxin, dabigatran, colchicine, pravastatin, methotrexate, rosuvastatin, sulfasalazine, metformin)	T	The effect of brigatinib on the pharmacokinetics of transporter substrates has not been studied.	Brigatinib is an inhibitor of P-gp, BCRP, OCT1, MATE1, and MATE2K *in vitro*. Patients should be closely monitored when ALUNBRIG is coadministered with substrates of these transporters with a narrow therapeutic index (e.g., digoxin, dabigatran, methotrexate).
Pharmacodynamic Interactions			
Agents that decrease heart rate (e.g., antiarrhythmics, beta adrenoceptor antagonists, non-dihydropyridine calcium channel blockers, digitalis glycosides, cholinesterase inhibitors, sphingosine-1 phosphate receptor modulators, HIV protease inhibitors, alpha$_2$-adrenoceptor agonists, and I_f blockers)	T	The effect of coadministration of agents that decrease heart rate with brigatinib has not been studied.	Coadministration of ALUNBRIG with agents that decrease heart rate should be avoided to the extent possible.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Brigatinib C_{max} was reduced by 13% with no effect on AUC in healthy subjects administered ALUNBRIG after a high-fat meal compared to the C_{max} and AUC after overnight fasting. ALUNBRIG may be taken with or without food.

Grapefruit or grapefruit juice may increase plasma concentrations of brigatinib and should be avoided.

9.6 Drug-Herb Interactions

St. John's Wort (*Hypericum perforatum*) is a strong CYP3A inducer. Coadministration of St. John's Wort with ALUNBRIG should be avoided (See **Table 8**).

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Brigatinib is a tyrosine kinase inhibitor (TKI) that targets ALK, in addition, it also demonstrates *in vitro* activities against ROS1, and insulin-like growth factor 1 receptor (IGF-1R). Brigatinib inhibited autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signalling protein STAT3 in *in vitro* and *in vivo* assays.

Brigatinib inhibited the *in vitro* proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins and demonstrated dose-dependent inhibition of EML4-ALK-positive NSCLC xenograft growth in mice.

At concentrations (≤ 500 nM) that are achieved clinically, brigatinib inhibited the *in vitro* viability of cells expressing EML4-ALK and 17 mutant forms associated with resistance to ALK inhibitors including crizotinib. Administration of brigatinib resulted in antitumor activity and prolonged survival in mice with an ALK-driven tumour cell line implanted intracranially.

Brigatinib demonstrated *in vivo* and clinical activity against multiple mutant forms of EML4-ALK, including G1202R and L1196M mutants identified in NSCLC tumours in patients who have progressed on crizotinib. In the Phase 2 ALTA study, baseline tumour tissue samples were evaluable in 17 of the 222 enrolled patients. Partial responses were seen in patients with and without secondary ALK kinase domain mutations, including one patient with a secondary ALK kinase domain mutation of G1202R.

10.2 Pharmacodynamics

Cardiac electrophysiology

The effects of brigatinib on the electrocardiogram were assessed in 123 patients with advanced malignancies following once daily ALUNBRIG doses of 30 mg to 240 mg. Serial ECG recordings were collected during steady-state treatment on Day 29. In patients receiving brigatinib 180 mg/day on Day 29 (N=61), the mean change from baseline at 2 h post-dosing was -6.0 bpm (90% CI -8.5, -3.4) for heart rate, 10.6 ms (90% CI 8.2, 13.0) for the PR interval, and 0.7 ms (90% CI -1.9, 3.3) for the QTcF interval. (See 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 9 DRUG INTERACTIONS, Agents that decrease heart rate.)

10.3 Pharmacokinetics

Absorption
Following administration of single oral doses of brigatinib of 30 to 240 mg, the median time to peak concentration (T_{max}) ranged from 1 to 4 hours postdose. The geometric mean (CV%) steady-state C_{max} of brigatinib at doses of 90 mg and 180 mg once daily was 552 (65%) and 1452 (60%) ng/mL, respectively, and the corresponding $AUC_{0\text{-}tau}$ was 8165 (57%) and 20276 (56%) h·ng/mL, respectively. After a single dose and repeat dosing of brigatinib, systemic exposure was dose proportional over the dose range of 60 mg to 240 mg once daily. The mean accumulation ratio after repeat dosing was 1.9 to 2.4.

Brigatinib C_{max} was reduced by 13% with no effect on AUC in healthy subjects administered ALUNBRIG after a high-fat meal compared to the C_{max} and AUC after overnight fasting.

Distribution:
Brigatinib is 91% bound to human plasma proteins and the binding is not concentration-dependent. The blood-to-plasma concentration ratio is 0.69. Following oral administration of brigatinib 180 mg once daily, the geometric mean apparent volume of distribution (V_z/F) at steady-state was 307 L.

Metabolism:
In vitro studies demonstrated that brigatinib is primarily metabolized by CYP2C8 and CYP3A4.

Following oral administration of a single 180 mg dose of [^{14}C]-brigatinib to healthy subjects, N-demethylation and cysteine conjugation were the two major metabolic clearance pathways. Unchanged brigatinib (92%) and its primary metabolite, AP26123 (3.5%), were the major circulating radioactive components. In patients, the steady-state AUC of AP26123 was less than 10% of brigatinib exposure. The metabolite, AP26123, inhibited ALK with approximately 3-fold lower potency than brigatinib *in vitro.*

Elimination
Following oral administration of brigatinib 180 mg once daily, the geometric mean apparent oral clearance (CL/F) of brigatinib at steady-state was 8.9 L/h. The clinically relevant mean plasma elimination half-life was 25 h, which is consistent with the observed accumulation ratio of 1.9 to 2.4.

Following administration of a single 180 mg oral dose of [^{14}C]-brigatinib to 6 healthy male subjects, 65% of the administered dose was recovered in feces and 25% of the administered dose was recovered in urine. Unchanged brigatinib represented 41% and 86% of the total radioactivity in feces and urine, respectively.

Special Populations and Conditions

- **Pediatrics:** No pediatric data have been made available to Health Canada; therefore,

Health Canada has not approved an indication for pediatric use

- **Geriatrics:** Population pharmacokinetic analyses showed that age had no clinically meaningful effect on the pharmacokinetics of brigatinib.

- **Sex:** Population pharmacokinetic analyses showed that sex had no clinically meaningful effect on the pharmacokinetics of brigatinib.

- **Ethnic Origin:** Population pharmacokinetic analyses showed that race had no clinically meaningful effect on the pharmacokinetics of brigatinib.

- **Hepatic Insufficiency:** Following a single dose of ALUNBRIG 90 mg, unbound brigatinib systemic exposure (AUC_{0-INF}) was 37% higher in subjects with severe hepatic impairment (Child-Pugh class C) compared to subjects with normal hepatic function. Unbound brigatinib systemic exposure (AUC_{0-INF}) was similar between subjects with mild (Child-Pugh class A) to moderate (Child-Pugh class B) hepatic impairment and subjects with normal hepatic function. (See 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations.)

- **Renal Insufficiency:** The pharmacokinetics of brigatinib was similar in patients with normal renal function (N=278) and in patients with mild (N=129) or moderate (N=36) renal impairment (CL_{cr} ≥ 30 mL/min) based on the results of population pharmacokinetic analyses. Following a single dose of ALUNBRIG 90 mg, unbound brigatinib systemic exposure (AUC_{0-INF}) was 86% higher in subjects with severe renal impairment (CL_{cr} < 30 mL/min) compared to subjects with normal renal function (CL_{cr} ≥ 90 mL/min). (See 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations.)

- **Obesity:** Population pharmacokinetic analyses showed that body weight had no clinically meaningful effect on the pharmacokinetics of brigatinib.

11 STORAGE, STABILITY AND DISPOSAL

Store between 15-30˚C
Keep in a safe place out of the reach of and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

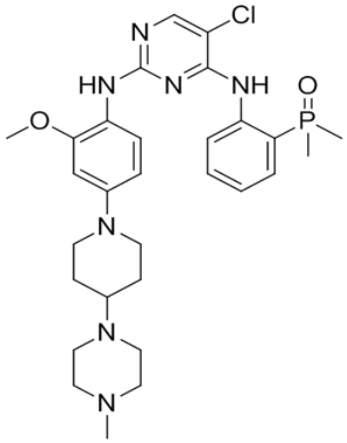
Drug Substance

Proper name: brigatinib

Chemical name: 5-chloro-N^4-[2-(dimethylphosphoryl)phenyl]-N^2-{2-methoxy-4[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine

Molecular formula and molecular mass: $C_{29}H_{39}ClN_7O_2P$ and 584.10

Structural formula:



Physicochemical properties: Brigatinib is an off-white to beige/tan solid with a melting point of 214°C. The pKas were determined to be: 1.73 ± 0.02 (base), 3.65 ± 0.01 (base), 4.72 ± 0.01 (base), and 8.04 ± 0.01 (base). The aqueous solubility of brigatinib is pH-dependent (i.e. aqueous solubility at pH of 2.5, is >165.2 mg/mL, at pH of 4.5, is >355.2 mg/mL, and at pH of 7.0, is 3.0 mg/mL). Brigatinib does not contain any chiral centers.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Advanced ALK-positive NSCLC in TKI-naïve patients (ALTA 1L Study)

The safety and efficacy of brigatinib was evaluated in a Phase 3 open-label, multicenter trial (ALTA 1L) in 275 adult patients with advanced ALK-positive NSCLC who had not previously received an ALK-targeted therapy with a documented ALK rearrangement based on a validated ALK testing. Patients were allowed to have up to 1 prior regimen of systemic anticancer therapy in the locally advanced or metastatic setting and had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2. Neurologically stable patients with treated or untreated central nervous system (CNS) metastases, including leptomeningeal metastases,

were eligible. Patients with a history of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis were excluded.

Patients were randomized in a 1:1 ratio to receive brigatinib 180 mg once daily with a 7-day lead-in at 90 mg once daily (n=137) or crizotinib 250 mg orally twice daily (n=138). Randomization was stratified by brain metastases (present, absent) and prior chemotherapy use for locally advanced or metastatic disease (yes, no). Patients in the crizotinib arm who experienced disease progression were offered to crossover to receive treatment with brigatinib.

The major efficacy outcome measure was progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by a Blinded Independent Review Committee (BIRC). Additional outcome measures as evaluated by the BIRC include confirmed overall response rate (ORR), duration of response (DOR), time to response, intracranial ORR, intracranial PFS, and intracranial DOR. Investigator-assessed outcomes include PFS and overall survival.

Baseline demographics and disease characteristics in ALTA 1L (**Table 9**) were median age 59 years old (range 27 to 89; 32% 65 and over), 59% White and 39% Asian, 55% female, 39% ECOG PS 0 and 56% ECOG PS 1 and 58% never smokers. The disease characteristics of the study population included: 93% Stage IV cancer, 27% prior chemotherapy in the locally advanced or metastatic setting, 14% prior radiation therapy to the brain, 31% bone metastases and 20% liver metastases. CNS metastases were present in 35% (n=96) of patients: of these, 41 patients had measurable CNS lesions as determined by a BIRC.

Table 9 Demographics and Disease Characteristics of ALK-positive Patients treated with ALUNBRIG and crizotinib in ALTA 1L

Characteristic	ALUNBRIG (n=137)	Crizotinib (n=138)	Total (N=275)
Sex, n (%)			
Male	68 (50)	57 (41)	125 (45)
Female	69 (50)	81 (59)	150 (55)
Age (years)			
Median (range)	58 (27-86)	60 (29-89)	59 (27-89)
≥65	44 (32)	43 (31)	87 (32)
<65	93 (68)	95 (69)	188 (68)
Race, n (%)			
White	76 (55)	86 (62)	162 (59)
Asian	59 (43)	49 (36)	108 (39)
Other	2 (2)	3 (2)	5 (2)
ECOG performance status, n (%)			
0	58 (42)	60 (44)	118 (43)

Characteristic	ALUNBRIG (n=137)	Crizotinib (n=138)	Total (N=275)
1	73 (53)	72 (52)	145 (53)
2	6 (4)	6 (4)	12 (4)
Smoking History, n (%)			
No	84 (61)	75 (54)	159 (58)
Yes	53 (39)	63 (46)	116 (42)
Disease Stage, n (%)			
Locally advanced (IIIB)	8 (6)	12 (9)	20 (7)
Metastatic (IV)	129 (94)	126 (91)	255 (93)
Histology, n (%)			
Adenocarcinoma	126 (92)	137 (99)	263 (96)
Squamous	4 (3)	0	4 (2)
Large cell	2 (2)	0	2 (1)
Adenosquamous Carcinoma	3 (2)	1 (1)	4 (2)
Other	2 (2)	0	2 (1)
CNS metastases at baseline*, n (%)			
Present	40 (29)	41 (30)	81 (30)
Sites of selected metastases at baseline*, n (%)			
Bone	36 (26)	50 (36)	86 (31)
Liver	31 (23)	24 (17)	55 (20)
Patients with prior radiotherapy to the brain, n (%)			
Yes	18 (13)	19 (14)	37 (13)
Prior chemotherapy in locally advanced or metastatic setting, n (%)			
Yes	36 (26)	37 (27)	73 (27)
No	101 (74)	101 (73)	202 (74)

* As assessed by the investigator

Advanced or metastatic ALK-positive NSCLC in previously crizotinib treated patients (ALTA Study)

The safety and efficacy of brigatinib was evaluated in an open-label, ongoing multicenter trial (ALTA, Phase 2) in 222 adult patients with metastatic ALK-positive NSCLC who had progressed on crizotinib. Eligibility criteria permitted enrollment of patients with a documented ALK rearrangement based on a validated ALK test, ECOG Performance Status of 0-2, prior chemotherapy, and central nervous system (CNS) metastases provided they were neurologically stable and did not require an increasing dose of corticosteroids. Patients with a history of pulmonary interstitial disease or drug-related pneumonitis were excluded.

Patients were randomized in a 1:1 ratio to receive brigatinib either 90 mg once daily (90 mg regimen, n=112) or 180 mg once daily with 7-day lead-in at 90 mg once daily (180 mg regimen, n=110). Disease assessments were conducted every 8 weeks from Cycles 3-15 and every

12 weeks thereafter. The median duration of follow-up was 17.9 months. Randomization was stratified by brain metastases (present, absent) and best prior response to crizotinib therapy (complete or partial response, any other response/unknown).

The primary outcome measure was confirmed objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by the investigator. Additional outcome measures included confirmed ORR as evaluated by an Independent Review Committee (IRC); time to response; progression-free survival (PFS); duration of response (DOR); disease control rate (DCR); overall survival; quality of life; and intracranial ORR, intracranial DOR and intracranial PFS as evaluated by an IRC.

Baseline demographics and disease characteristics in ALTA are shown in (**Table 10**). In this study, 95% patients were never or former smokers, and 98% had Stage IV disease. The most common sites of extra-thoracic metastasis included 69% brain (of whom 62% had received prior radiation to the brain), 40% bone, and 26% liver.

Table 10 Demographics and Disease Characteristics of ALK-Positive Patients treated with ALUNBRIG in ALTA

Characteristic	90 mg qd (n=112)	90 mg → 180 mg qd (n=110)	Total (N=222)
Sex, n (%)			
Male	50 (44.6)	46 (41.8)	96 (43.2)
Female	62 (55.4)	64 (58.2)	126 (56.8)
Age (years)			
Median (range)	51 (18-82)	57 (20-81)	54 (18-82)
Race, n (%)			
White	72 (64.3)	76 (69.1)	148 (66.7)
Asian	39 (34.8)	30 (27.3)	69 (31.1)
Other	1 (0.9)	4 (3.6)	5 (2.3)
ECOG performance status, n (%)			
0	34 (30.4)	45 (40.9)	79 (35.6)
1	71 (63.4)	56 (50.9)	127 (57.2)
2	7 (6.3)	9 (8.2)	16 (7.2)
Smoking History, n (%)			
No	71 (63.4)	63 (57.3)	134 (60.4)
Yes	40 (35.8)	47 (42.7)	87 (39.2)
Unknown	1 (0.9)	0 (0.0)	1 (0.5)
Histology, n (%)			
Adenocarinoma	107 (95.5)	108 (98.2)	215 (96.8)
Squamous	2 (1.8)	1 (0.9)	3 (1.4)
Large cell	1 (0.9)	1 (0.9)	2 (0.9)

Characteristic	90 mg qd (n=112)	90 mg → 180 mg qd (n=110)	Total (N=222)
Adenosquamous	1 (0.9)	0 (0.0)	1 (0.5)
Mucoepidermoid	1 (0.9)	0 (0.0)	1 (0.5)
Brain metastases at base line, n (%)			
Present	80 (71.4)	74 (67.3)	154 (69.4)
Prior chemotherapy, n (%)			
Yes	83 (74.1)	81 (73.6)	164 (73.9)
Best response to prior crizotinib, n (%)			
PR or CR	71 (63.4)	73 (66.4)	144 (64.9)
Other response or unknown	41 (36.6)	37 (33.6)	78 (35.1)

14.2 Study Results

Advanced ALK-positive NSCLC in TKI-naïve patients (ALTA 1L Study)

The efficacy results from ALTA 1L (Phase 3) analysis are summarized in **Table 11** and **Figure 1**.

Table 11 Efficacy Results by BIRC Assessment in ALTA IL (ITT Population at interim analysis)[a]

Efficacy Parameters	ALUNBRIG N = 137	Crizotinib N = 138
PFS (BIRC)		
Number of Patients with Events, n (%)	63 (46)	87 (63)
Median (in months) (95% CI)	24 (18.5, NE)	11 (9.2, 12.9)
Hazard ratio (95% CI)	0.49 (0.35, 0.68)	
Log-rank p-value[b]	<0.0001	
Confirmed Objective Response Rate (BIRC)		
Responders, n (%) (95% CI)	101 (73.7) (65.5, 80.9)	85 (61.6) (52.9, 69.7)
p-value[b,c]	0.0342	
Complete Response, % (95% CI)	14.6 (9.2, 21.6)	8.7 (4.6, 14.7)
Partial Response, % (95% CI)	59.1 (50.4, 67.4)	52.9 (44.2, 61.5)
Duration of Confirmed Response (BIRC)		
Responders, n (%)	101 (73.7)	85 (61.6)
Median (months) (95% CI)	NE (19.4, NE)	13.8 (9.3, 20.8)
Response duration at 24 months, %	51.3	29.6

BIRC = Blinded Independent Review Committee; NE = Not Estimable; CI = Confidence Interval

[a] The median follow up for ALUNBRIG arm was 24.9 months

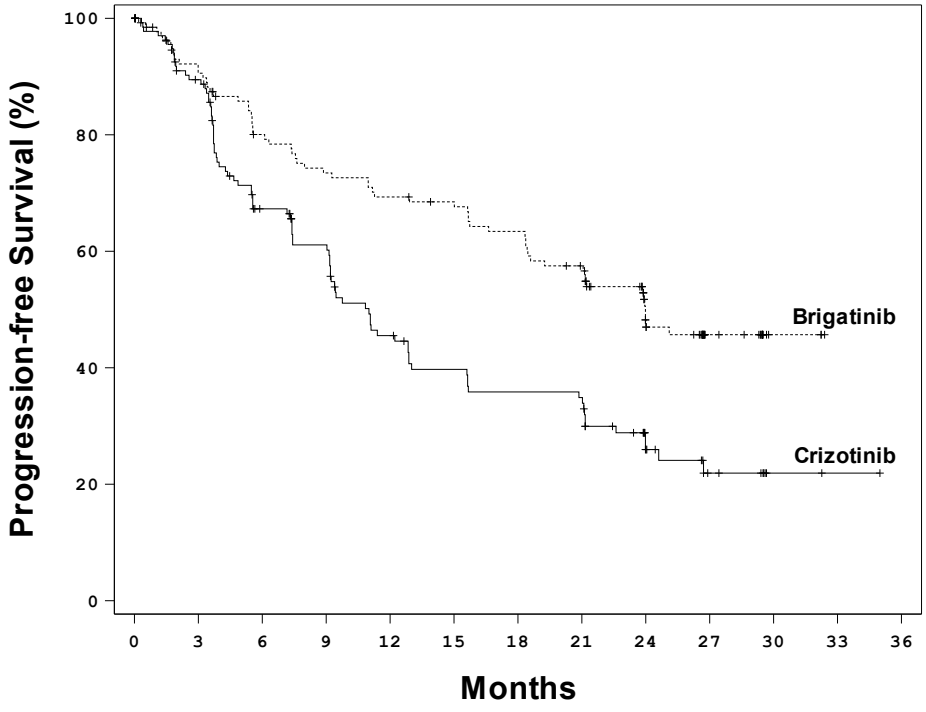
[b] Stratified by presence of iCNS metastases at baseline and prior chemotherapy for locally advanced or metastatic disease for log-rank test and Cochran Mantel-Haenszel test, respectively

[c] From a Cochran Mantel-Haenszel test

At primary analysis, the ALTA 1L study met its primary endpoint demonstrating a statistically significant improvement in PFS by BIRC. The median duration of follow-up was 24.9 months (range: 0 – 34.1) in the brigatinib arm and 15.2 months (range: 0.1 – 36) for the crizotinib arm, respectively.

At the final analysis, with a median follow-up of the brigatinib arm at 40.4 months, overall survival was immature (Hazard ratio = 0.81 [95% CI (0.53, 1.22)]). Forty seven percent patients crossed over from crizotinib arm to brigatinib arm. In confirmed responders, the median duration of response was 33.2 months [CI: 22.1; NE] in the brigatinib arm vs 13.8 months (95% CI: 10.4; 22.1) in the crizotinib arm.

Figure 1. Kaplan-Meier Plot of Progression-Free Survival by BIRC in ALTA 1L



Number at Risk												
Brigatinib	137	114	97	89	84	81	75	66	39	18	3	
Crizotinib	138	116	80	68	49	41	37	36	17	8	2	1

Duration of intracranial response was measured from date of first intracranial response until intracranial disease progression (new lesions, intracranial target lesion diameter growth ≥20% from nadir, or unequivocal progression of intracranial nontarget lesions) or death.

BIRC assessment of intracranial efficacy in patients with measurable brain metastases (≥10 mm in longest diameter) at baseline are summarized in **Table 12**.

Table 12 BIRC-assessed Intracranial Efficacy in Patients with Measurable CNS Metastases at Baseline in ALTA 1L

	ALUNBRIG N = 18	Crizotinib N = 23
Intracranial Objective Response Rate		
Responders, n (%) (95% CI)	14 (77.8) (52.4, 93.6)	6 (26.1) (10.2, 48.4)
p-value[a,b]	0.0014	
Complete Response %	27.8	0
Partial Response, %	50	26.1
Duration of Intracranial Response[c]		
Responders, n (%)	14 (77.8)	6 (26.1)
Median (months) (95% CI)	NE (5.7, NE)	9.2 (3.9, 9.2)
Intracranial response duration at 24 months, %	64.3	NE

CI = Confidence Interval; NE = Not Estimable

[a] Stratified by presence prior chemotherapy for locally advanced or metastatic disease for log-rank test and Cochran Mantel-Haenszel test, respectively

[b] From a Cochran Mantel-Haenszel test

[c] measured from date of first confirmed intracranial response until date of intracranial disease progression (new intracranial lesions, intracranial target lesion diameter growth ≥ 20% from nadir, or unequivocal progression of intracranial nontarget lesions) or death or censoring

The PFS for patients with CNS metastases at baseline (Median PFS for brigatinib = 24 months, 95% CI: 18.37-NE, median PFS for crizotinib = 5.6 months, 95% CI: 3.84-9.4), HR = 0.25, 95% CI: 0.14-0.46.

Advanced or metastatic ALK-positive NSCLC in previously crizotinib treated patients (ALTA Study)

Investigator-assessed and Independent Review Committee (IRC) assessed systemic efficacy results from ALTA (Phase 2) analysis are summarized in **Table 13**.

Table 13 Efficacy Results in ALTA (ITT Population)

Efficacy Parameters	Investigator Assessment		IRC Assessment	
	90 mg regimen* N = 112	180 mg regimen† N = 110	90 mg regimen* N = 112	180 mg regimen† N = 110
Objective Response Rate				
(%)	45.5%	55.5%	50.9%	54.5%
95% CI‡	(36.1, 55.2)	(45.7, 64.9)	(41.3, 60.5)	(44.8, 64.1)
Complete Response (%)	1.8%	4.5%	5.4%	5.5%

Efficacy Parameters	Investigator Assessment		IRC Assessment	
	90 mg regimen* N = 112	180 mg regimen† N = 110	90 mg regimen* N = 112	180 mg regimen† N = 110
Partial Response (%)	43.8%	50.9%	45.5%	49.1%
Duration of response				
Median (months)	12.0	13.8	13.8	14.8
95% CI	(9.2, 17.7)	(10.2, 17.5)	(7.4, NE)	(12.6, NE)

CI = Confidence Interval; NE = Not Estimable
*90 mg once daily regimen
†180 mg once daily with 7-day lead-in at 90 mg once daily
‡Confidence Interval for investigator assessed ORR is 97.5% and for IRC assessed ORR is 95%

The investigator-assessed PFS for the 90 mg regimen and 180 mg regimen was 9.2 months (95% CI: 7.4, 11.1) and 15.6 months (95% CI: 11.1, 19.4), respectively. The IRC-assessed PFS for the 90 mg regimen and 180 mg regimen was 9.2 months (95% CI: 7.4, 12.8) and 16.7 months (95% CI: 11.6, Not estimable), respectively.

IRC assessments of intracranial ORR and duration of intracranial response in patients from ALTA with measurable brain metastases (≥10 mm in longest diameter) at baseline are summarized in **Table 14**.

Table 14 Intracranial Efficacy in Patients with Measurable Brain Metastases at Baseline in ALTA IRC-assessed efficacy parameter

IRC-assessed efficacy parameter	**Patients with Measurable Brain Metastases at Baseline**	
	90 mg regimen* (N=26)	**180 mg regimen† (N=18)**
Intracranial Objective Response Rate		
(%)	50.0%	66.7%
95% CI	(29.9, 70.1)	(41.0, 86.7)
Complete Response Rate	7.7%	0.0%
Partial Response Rate	42.3%	66.7%
Duration of Intracranial Response‡		
Median (months)	NE	16.6
Range	2.0-19.4+	1.9-16.6

CI = Confidence Interval; NE = Not Estimable
*90 mg once daily regimen
†180 mg once daily with 7-day lead-in at 90 mg once daily
‡Events include intracranial disease progression (new lesions, intracranial target lesion diameter growth ≥20% from nadir, or unequivocal progression of intracranial non-target lesions) or death.

Geriatrics

Of the total number of patients in a Phase 2 study (N = 222) with metastatic ALK-positive NSCLC who had progressed on crizotinib (ALTA), 19% were 65-74 years and 4.1% were 75 years or older. No clinically relevant differences in safety or efficacy were observed between patients ≥65 and younger patients. No efficacy data are available in patients over 85 years of age. (See 4 DOSAGE AND ADMINISTRATION.)

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Animal Toxicology

Nonclinical safety assessment in rats and monkeys identified potential risk for toxicity in multiple organs such as gastrointestinal system, bone marrow, eyes, testes, liver, kidney, bone, and heart. These effects were generally reversible during the non-dosing recovery period; however, effects in the eyes and testes were notable exceptions due to lack of recovery.

Carcinogenicity: Carcinogenicity studies have not been performed with ALUNBRIG.

Genotoxicity: Brigatinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) or the mammalian cell chromosomal aberration assays, but slightly increased the number of micronuclei in a rat bone marrow micronucleus test. The mechanism of micronucleus induction was abnormal chromosome segregation (aneugenicity) and not a clastogenic effect on chromosomes. This effect was observed at approximately 5-fold the human exposure at the 180 mg once daily dose. Therefore, genotoxic risk is not expected in humans.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrALUNBRIG®

Brigatinib Tablets

Read this carefully before you start taking **ALUNBRIG** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ALUNBRIG**.

Serious Warnings and Precautions

ALUNBRIG can cause severe side effects which include:

- **Serious lung problems** (such as **Interstitial Lung Disease or Pneumonitis**), which can cause breathing problems, shortness of breath, cough, or fever that may result in death.
- **Hypertension** which is high blood pressure
- **Elevation of pancreatic enzymes** which is an increase in the levels of amylase or lipase in the blood. This can cause weight loss, nausea or abdominal pain that gets worse with eating.
- **Hyperglycemia** which is increased sugar in the blood
- **Creatine phosphokinase (CPK) elevation** which means there is a higher than normal level of CPK in the blood. This can cause muscle pain, tenderness or weakness.

ALUNBRIG should only be prescribed by doctors who are experienced in the use of drugs to treat cancer.

What is ALUNBRIG used for?

ALUNBRIG is used to treat adults with non-small cell lung cancer (NSCLC) that is caused by a change in the anaplastic lymphoma kinase (ALK) gene (called ALK-positive). These patients will have ALK-positive NSCLC that has grown outside of the lung (called locally advanced) or has spread to other parts of the body (called metastatic). A test is done to find out if there is a change in the ALK-gene.

For these patients, their disease:

- cannot be cured with surgery or other treatment (like chemotherapy or radiation); and
- will not have been previously treated.

ALUNBRIG is also used in patients whose cancer has gotten worse after taking crizotinib or in patients who are unable to take crizotinib.

How does ALUNBRIG work?
ALUNBRIG may slow or stop the growth of lung cancer if the cancer is caused by a change in a gene called anaplastic lymphoma kinase (ALK). By doing so, ALUNBRIG may slow down the growth and spread of non-small cell lung cancer (NSCLC).

What are the ingredients in ALUNBRIG?
Medicinal ingredients: brigatinib
Non-medicinal ingredients: lactose monohydrate, magnesium stearate, microcrystalline cellulose, silica colloidal hydrophobic, sodium starch glycolate (type A). The tablet coating consists of polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

ALUNBRIG comes in the following dosage forms:
Tablets: 30 mg, 90 mg, and 180 mg

Do not use ALUNBRIG if:
- you are allergic to brigatinib or any of the other ingredients in ALUNBRIG

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ALUNBRIG. Talk about any health conditions or problems you may have, including if you:
- have problems with your lungs or problems breathing
- have problems with your heart including slow heart rate
- have problems with high blood pressure
- are taking medicines to lower your blood pressure or control your heart rate
- have problems with your vision
- have problems with your muscles including muscle pain, tenderness, or weakness
- have or have had problems with your pancreas
- have or have had problems with your kidneys
- have or have had problems with your liver
- have diabetes or high blood sugar
- are pregnant
- think you may be pregnant
- you and your partner plan on becoming pregnant
- are breast-feeding or plan to breast-feed
- are younger than 18 years of age. The effects of ALUNBRIG in people younger than 18 years old are not known
- are intolerant to lactose, as ALUNBRIG contains lactose.

Tell your healthcare professional immediately if, during your treatment with ALUNBRIG, you experience any new or worsening symptoms as follows:
- Cough with or without mucous, fever, chest pain, trouble breathing or shortness of breath, especially in the first week of treatment. These may be signs of serious lung problems.
- Slowing of your heart rate, severe headache, or if you feel dizzy, lightheaded, or faint during

treatment. These may be signs of heart or blood pressure problems.
- Weight loss or nausea, or abdominal pain that gets worse with eating and may spread to the back. These may be signs of problems with your pancreas.
- You become very thirsty or urinate frequently. These may be signs of a high level of sugar in the blood.
- Unexplained muscle pain or muscle pain that does not go away, tenderness or weakness. These may be signs of muscle problems.
- Pain on the right side of your stomach area, yellowing of your skin or the whites of your eyes, or dark urine. These may be signs of problems with your liver.
- Blurred vision, seeing double, have difficultly seeing in bright light, see flashes of light or loss of vision. These may be signs of eye problems.

Other warnings you should know about:
- ALUNBRIG should only be used by people whose lung cancer is caused by a change in a gene called anaplastic lymphoma kinase (ALK). Before you start taking ALUNBRIG, you should have had your cancer tested for this change.
- Do not drive or use machines or tools if you feel tired or dizzy or have problems with your vision while taking ALUNBRIG.
- ALUNBRIG can cause your skin to become very sensitive to sunlight. You should avoid prolonged exposure to the sun or tanning beds while you are taking ALUNBRIG and for 5 days after your last dose. When you are in the sun, wear protective clothing, a hat, a broad spectrum UVA/UVB sunscreen and lip balm with a Sun Protection Factor (SPF) of at least 30. These will, protect against sunburn.

Fertility in men
ALUNBRIG may lower fertility in men. Talk to your healthcare professional if you are planning to father a child in the future.

Pregnancy and breast-feeding
- **Pregnant women**
  ALUNBRIG may harm an unborn baby. You must tell your healthcare professional if you are or think you may be pregnant. Ask your healthcare professional for advice if you are planning to have a baby.

- **Breast-feeding mothers**
  Do not use ALUNBRIG while breast feeding and for at least 1 week after stopping treatment.

Birth control in men and women
- **Women**
  During your ALUNBRIG treatment, do not become pregnant. Use a highly effective, non hormonal birth control method, during treatment and for 4 months after stopping ALUNBRIG. Hormonal forms of birth control such as oral contraceptives (birth control pills)

may not be effective if used during treatment with ALUNBRIG. Talk to your healthcare professional for advice on effective methods of birth control.

- **Men**
  Do not father a child during your ALUNBRIG treatment and for 3 months after stopping treatment. Use condoms if you have sex while receiving ALUNBRIG and for 3 months after stopping treatment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ALUNBRIG:

- **ketoconazole, itraconazole, voriconazole, fluconazole**: medicines to treat fungal infections
- **efavirenz, etravirine, indinavir, nelfinavir, ritonavir, saquinavir, cobicistat**: medicines to treat HIV infection
- **boceprevir, telaprevir**: medicines to treat hepatitis C infection
- **clarithromycin, nafcillin, telithromycin, troleandomycin, ciprofloxacin, erythromycin**: medicines to treat bacterial infections
- **bosentan, diltiazem, verapamil**: medicines to treat irregular heart rhythm and high blood pressure
- **drugs that lower heart rate**: antiarrhythmics, beta adrenoceptor antagonists, non-dihydropyridine calcium channel blockers, digitalis glycosides, cholinesterase inhibitors, sphingosine-1 phosphate receptor modulators, alpha$_2$-adrenoceptor agonists, and I_f blockers
- **nefazodone**: a medicine to treat depression
- **St. John's wort**: an herbal product used to treat depression. It is also known as hypericum perforatum.
- **ergot alkaloids**: medicines used to treat throbbing headaches, such as migraines and cluster headaches
- **fentanyl**: a medicine to treat pain
- **modafinil**: a medicine to treat excessive sleepiness
- **carbamazepine**: a medicine to treat epilepsy, euphoric/depressive episodes and certain pain conditions
- **phenobarbital, phenytoin**: medicines to treat epilepsy
- **pimozide**: a medicine to treat schizophrenia
- **quetiapine**: a medicine to treat schizophrenia, bipolar disorder, and depression
- **rifabutin, rifampicin**: medicines to treat tuberculosis or certain other infections
- **digoxin**: a medicine to treat heart weakness
- **dabigatran**: a medicine to inhibit blood clotting
- **colchicine**: a medicine to treat gout attacks
- **cisapride**: a medicine to treat heartburn
- **pravastatin, rosuvastatin, simvastatin**: medicines to lower cholesterol levels
- **methotrexate**: a medicine to treat severe joint inflammation, cancer, and the skin disease

psoriasis
- **sulfasalazine**: a medicine to treat severe bowel and rheumatic joint inflammation
- **cyclosporine**: a medicine to treat severe bowel and joint inflammation, and the skin disease psoriasis
- **sirolimus, tacrolimus**: medicines used after an organ transplant
- **metformin**: a medicine to treat diabetes
- **estrogen, progestogen**: hormonal birth control such as the pill, the patch, hormone-containing intrauterine device, or vaginal ring.
- **grapefruit and grapefruit juice**

How to take ALUNBRIG:
- Always take ALUNBRIG exactly as your doctor or pharmacist has told you. Check with your healthcare professional if you are not sure.
- ALUNBRIG is taken by mouth. Swallow each tablet whole with water. Do not crush or chew the tablets.
- ALUNBRIG may be taken with or without food.

Usual dose:
- Take the 90 mg tablet of ALUNBRIG once a day for the first 7 days of treatment. Then take the 180 mg tablet once a day.
- If you are taking certain medications or are feeling unwell, your doctor may:
  - start you on a different dose
  - lower your dose
  - stop your treatment for a short time, or
  - stop your treatment completely

Overdose:

If you think you, or a person you are caring for, have taken too much ALUNBRIG, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take ALUNBRIG:
- Take your next dose at your regular time
- Do not take a double dose to make up for your missed dose

Vomiting:

- If you vomit (throw up) after taking ALUNBRIG, do not take an extra dose of ALUNBRIG. Just take your next dose at the usual time.

What are possible side effects from using ALUNBRIG?

These are not all the possible side effects you may have when taking ALUNBRIG. If you experience any side effects not listed here, tell your healthcare professional.

- Abdominal pain also called abdominal discomfort, nausea, vomiting, diarrhea, constipation, acid reflux
- Cold-like symptoms
- Dry mouth
- Inflammation of the mouth, lips and other mucous membranes
- Indigestion
- Decreased appetite
- Taste disturbance
- Rash
- Acne or pimples
- Dry skin
- Itchy skin
- Skin sensitivity to the sun
- Muscle spasms
- Muscle and/or bone stiffness
- Pain including joint, muscle, chest, abdomen and pain in back, arms and legs
- Fatigue
- Weakness
- Swelling caused by excess fluid
- Cough
- Shortness of breath
- Headache
- Dizziness
- Trouble sleeping
- Depression
- Impairment or change in voice quality
- Fever
- Numbness and tingling in the hands and feet
- Weight gain

Your healthcare professional will conduct tests before you start taking ALUNBRIG and regularly during your treatment. These tests will include measurements of your blood pressure and heart rate. You will also have blood tests. ALUNBRIG can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results. These results will tell your healthcare professional how ALUNBRIG is affecting your muscles, liver and pancreas.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Hypertension (high blood pressure): headaches, dizziness, blurred vision, chest pain or shortness of breath		√	
Increased blood levels of amylase or lipase: weight loss or nausea, or abdominal pain that gets worse with eating and may spread to the back		√	
Increased blood levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT): pain on the right side of your stomach area, yellowing of your skin or the whites of your eyes, or dark urine		√	
Increased blood level of creatine phosphokinase: unexplained muscle pain, tenderness or weakness		√	
Hyperglycemia (increased blood sugar): frequent urination, thirst, and hunger		√	
Serious Lung Problems (such as pneumonia, pneumonitis, interstitial lung disease): new or worsening difficulty breathing, chest pain, shortness of breath, cough with or without mucous, or fever			√
Vision Problems: loss or change in vision		√	
Anemia (decrease in number of red blood cells): dizziness, feeling tired and weak, loss of energy, shortness of breath		√	
Neutropenia (decrease in number of white blood cells): aches, feeling tired, fever, flu-like symptoms, infections		√	
Lymphopenia (decrease in number of lymphocytes): infections		√	
Nausea	√		
Vomiting	√		

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Diarrhea: loose or watery and frequent stools	√		
COMMON			
Pyrexia: fever	√		
Bradycardia (slow heartbeat): chest pain or discomfort, changes in heartbeat, dizziness, light-headedness or fainting		√	
Stomatitis: mouth sores	√		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store ALUNBRIG between 15-30˚C

Keep out of reach and sight of children.

If you want more information about ALUNBRIG:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website http://www.takeda.com/en-ca/alunbrigpm, or by calling 1-800-268-2772.

This leaflet was prepared by Takeda Canada Inc., Toronto, Ontario M5H 4E3.

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