PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrALUNBRIG™

Brigatinib Tablets

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

Protein Kinase Inhibitor (L01XE)

ALUNBRIG™ (brigatinib) has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for ALUNBRIG™, please refer to Health Canada's Notice of Compliance with conditions - drug products web site.

ALUNBRIG™ (brigatinib) is indicated 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).

Takeda Canada Inc.
22 Adelaide Street West, Suite 3800
Toronto Ontario M5H 4E3
www.takeda.com/en-ca

Date of Initial Approval:
25 July 2018

Date of Revision:
28 November 2019

Submission Control No:

This product has been authorized under the Notice of Compliance with Conditions (NOC/c) policy.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market-authorization issued to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada. Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention, or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that Sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol **NOC/c**. These sections may include, but are not limited to, the following:

Indications and Clinical Use;
Action and Clinical Pharmacology;
Warnings and Precautions;
Adverse Reactions;
Dosage and Administration; and
Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to the Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the Sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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Pr ALUNBRIG™

Brigatinib Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

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ALUNBRIG™ (brigatinib) is indicated 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).

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Oral	Tablet/ 30mg, 90 mg, 180 mg	Lactose Monohydrate *For a complete listing, see Dosage Forms, Strengths, Composition and Packaging section.*

NOC/c 1 INDICATIONS AND CLINICAL USE

ALUNBRIG™ (brigatinib) is indicated 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).

Geriatrics

Geriatrics (≥ 65 years of age):
Of the 222 patients in the pivotal trial, 23% 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 WARNINGS AND PRECAUTIONS, Respiratory.)

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.

NOC/c

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 Dosage Forms, Strengths, Composition and Packaging.

NOC/c

3 DOSAGE AND ADMINISTRATION

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.

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

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

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 modification levels 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.
	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

Adverse Reaction	Severity*	ALUNBRIG™ Dosing
		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 CPK elevation (> 5.0 × ULN)	• Withhold ALUNBRIG™ until recovery to Grade ≤1 (≤ 2.5 × ULN) or to baseline, then resume ALUNBRIG™ at same dose. • Recurrence: Withhold ALUNBRIG™ until recovery to Grade ≤ 1 (≤ 2.5 × ULN) or to baseline, then resume ALUNBRIG™ at next lower dose (Table 1).
	Grade 4 CPK elevation (> 10.0 × ULN)	• Withhold ALUNBRIG™ until recovery to Grade ≤ 1 (≤ 2.5 × ULN) or to 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.

Adverse Reaction	Severity*	ALUNBRIG™ Dosing
	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).
	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 CYP3A Inhibitors: The concomitant use of ALUNBRIG™ with strong CYP3A inhibitors should be avoided. If concomitant use of strong CYP3A inhibitors cannot be avoided, the dose of ALUNBRIG™ should be reduced 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. (See DRUG INTERACTIONS, Drug-Drug Interactions.)

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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations.)

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.

Hepatic Impairment: No dose adjustment of ALUNBRIG™ is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or total bilirubin > 1-1.5 x ULN and any AST) based on population pharmacokinetic analyses. Available data do not indicate a clinically meaningful effect of mild hepatic impairment on the safety and efficacy of ALUNBRIG™. The pharmacokinetics and safety of ALUNBRIG™ in patients with moderate or severe hepatic impairment have not been studied. In the absence of data, the use of ALUNBRIG™ is not recommended in patients with moderate or severe hepatic impairment. (See ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations.)

Renal Impairment: No dose adjustment of ALUNBRIG™ is recommended for patients with mild or moderate renal impairment (creatinine clearance ≥ 30 mL/min) based on population

pharmacokinetic analyses. Available data do not indicate a clinically meaningful effect of mild or moderate renal impairment on the safety and efficacy of ALUNBRIG™. The pharmacokinetics and safety of ALUNBRIG™ in patients with severe renal impairment (creatinine clearance < 30 mL/min) have not been studied. In the absence of data, the use of ALUNBRIG™ is not recommended in patients with severe renal impairment. (See ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations.)

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.

4 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 ADVERSE REACTIONS.)

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

5 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)

NOC/c

6 WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Pulmonary Adverse Reactions (see WARNINGS AND PRECAUTIONS, Respiratory)
- Hypertension (see WARNINGS AND PRECAUTIONS, Cardiovascular)
- Elevation of pancreatic enzymes (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic)
- Hyperglycemia (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism)
- Creatine phosphokinase (CPK) elevation (see WARNINGS AND PRECAUTIONS, Musculoskeletal)

ALUNBRIG™ (brigatinib) has not been studied in patients with moderate to severe hepatic impairment or severe renal impairment. (See WARNINGS AND PRECAUTIONS, Special Populations.)

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

General

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

Drug Interactions

The concomitant use of ALUNBRIG™ with strong CYP3A inhibitors should be avoided. If concomitant use of strong CYP3A inhibitors cannot be avoided, the dose of ALUNBRIG™ should be reduced 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. (See DRUG INTERACTIONS.)

The concomitant use of ALUNBRIG™ with strong and moderate CYP3A inducers should be avoided. (See DRUG INTERACTIONS.)

Brigatinib is an inducer of CYP3A *in vitro*. Brigatinib may reduce plasma concentrations of coadministered medications that are predominantly metabolized by CYP3A. Brigatinib may also induce other enzymes and transporters (e.g., CYP2C, P-gp) via the same mechanisms responsible for induction of CYP3A (e.g., pregnane X receptor activation). (See 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 NON-CLINICAL TOXICOLOGY.)

Cardiovascular

Bradycardia

Bradycardia, sinus bradycardia, and prolongation of the PR interval has occurred in patients treated with ALUNBRIG™ in Phase 1 and Phase 2 (ALTA) 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 Monitoring and Laboratory Tests; ADVERSE REACTIONS; ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology.)

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

Hypertension

Hypertension including Grade 3 hypertension as well as hypertensive retinopathy has occurred in 19% of patients treated with ALUNBRIG™. (See ADVERSE REACTIONS.)

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 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
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 ADVERSE REACTIONS; DOSAGE AND ADMINISTRATION.)

Hepatic/Biliary/Pancreatic

Elevations of pancreatic enzymes
Elevations of amylase and lipase have occurred in patients treated with ALUNBRIG™. 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 DOSAGE AND ADMINISTRATION; ADVERSE REACTIONS.)

Musculoskeletal

Creatine phosphokinase (CPK) elevation
Elevations of CPK have occurred in patients treated with ALUNBRIG™. 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 ADVERSE REACTIONS; DOSAGE AND ADMINISTRATION.)

Ophthalmologic

Visual disturbance
Visual disturbance adverse reactions have occurred in patients treated with ALUNBRIG™. Patients should be advised to report any visual symptoms. For new or worsening severe visual symptoms, an ophthalmologic evaluation and dose reduction should be considered. (See ADVERSE REACTIONS; DOSAGE AND ADMINISTRATION.)

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 ADVERSE REACTIONS.)

In ALTA, 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.

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 WARNINGS AND PRECAUTIONS, Special Populations.) Patients with a history of ILD or drug-induced pneumonitis were excluded from ALTA.

Additionally, 2.3% of patients experienced pneumonitis following the second week of treatment, with 2 patients having Grade 3 pneumonitis. (See DOSAGE AND ADMINISTRATION.)

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 DOSAGE AND ADMINISTRATION.)

Sexual Health

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 WARNING

AND PRECAUTIONS, Special Populations; ACTION AND CLINICAL PHARMACOLOGY.)

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.

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 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 WARNINGS AND PRECAUTIONS, Cardiovascular; DOSAGE AND ADMINISTRATION.)

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 WARNINGS AND PRECAUTIONS, Musculoskeletal; DOSAGE AND ADMINISTRATION.)

Pancreatic Enzyme Monitoring
Lipase and amylase should be monitored regularly during treatment with ALUNBRIG™. (See WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; DOSAGE AND ADMINISTRATION; ADVERSE REACTIONS.)

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 WARNINGS AND PRECAUTIONS, Endocrine and metabolism; DOSAGE AND ADMINISTRATION; ADVERSE REACTIONS.)

Special Populations

6.1.1 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 WARNINGS AND PRECAUTIONS, Sexual Health.)

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.

6.1.2 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.

6.1.3 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 222 patients in the pivotal trial, 23% were 65 years of age and older. The 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 WARNINGS AND PRECAUTIONS, Respiratory.)

6.1.4 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.

6.1.5 Hepatic Impairment

No dose adjustment of ALUNBRIG™ is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or total bilirubin > 1-1.5 x ULN and any AST). The pharmacokinetics of brigatinib was similar in patients with normal hepatic function and in patients with mild hepatic impairment based on the results of population pharmacokinetic analyses. Available data do not indicate a clinically meaningful effect of mild hepatic impairment on the safety and efficacy of ALUNBRIG™. The pharmacokinetics and safety of ALUNBRIG™ in patients with moderate or severe hepatic impairment have not been studied. In the absence of data, the use of ALUNBRIG™ is not recommended in patients with moderate or severe hepatic impairment. (See ACTION AND CLINICAL PHARMACOLOGY, Special Populations.)

6.1.6 Renal Impairment

No dose adjustment of ALUNBRIG™ is recommended for patients with mild or moderate renal impairment (creatinine clearance ≥ 30 mL/min). The pharmacokinetics of brigatinib was similar in patients with normal renal function and in patients with mild or moderate renal impairment (creatinine clearance ≥ 30 mL/min) based on the results of population pharmacokinetic analyses. Available data do not indicate a clinically meaningful effect of mild or moderate renal impairment on the safety and efficacy of ALUNBRIG™. The pharmacokinetics and safety of ALUNBRIG™ in patients with severe renal impairment (creatinine clearance < 30 mL/min) have not been studied. In the absence of data, the use of ALUNBRIG™ is not recommended in patients with severe renal impairment. (See ACTION AND CLINICAL PHARMACOLOGY, Special Populations.)

NOC/c

7 ADVERSE REACTIONS

Adverse Reaction Overview

In a randomized, 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 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 10.9% (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]).

Clinical Trial Adverse Reactions

Table 4 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 (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Metabolism and Nutrition Disorders				
Decreased appetite	28 (26)	1 (0.9)	26 (24)	1 (0.9)
Psychiatric Disorders				
Insomnia	18 (17)	0	10 (9.1)	0
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
Eye Disorders				
Visual Disturbance§	9 (8.3)	0	18 (16)	2 (1.8)
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
Vascular Disorders				
Hypertension	19 (17)	6 (5.5)	30 (27)	9 (8.2)
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)
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⊳	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)
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)

Adverse Reactions	90 mg once daily N = 109		90→180 mg once daily N = 110	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
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)
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)

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
†Includes headache and sinus headache
‡Includes peripheral sensory neuropathy and paresthesia
§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
¶ Includes bradycardia and sinus bradycardia
#Includes dyspnea and exertional dyspnea
ÞIncludes abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort
**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)
‡‡Includes musculoskeletal pain and myalgia
§§ Based on laboratory assessment
¶¶Includes asthenia and fatigue
##Includes face edema, edema peripheral, periorbital edema, and swelling face

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

Table 5 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 (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
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)
Blood creatinine increased‡	12 (11)	0	16 (15)	0
Hematology				
Anemia	36 (33)	1 (0.9)	54 (49)	2 (1.8)
Lymphopenia	33 (30)	5 (4.6)	44 (40)	14 (13)
Decreased white blood cell count	20 (18)	0	26 (24)	0

*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

Additional Safety Information from Clinical Trial Experience

Pulmonary Adverse Reactions
In ALTA, 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 DOSAGE AND ADMINISTRATION; WARNINGS AND PRECAUTIONS.)

In ALTA, 13.5% 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 DOSAGE AND ADMINISTRATION; 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. In a separate dose finding study (Study 101), a decrease in heart rate was associated with increased ALUNBRIG™ plasma concentrations (C_{max}). (See DOSAGE AND ADMINISTRATION; 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 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 DOSAGE AND ADMINISTRATION; 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 DOSAGE AND ADMINISTRATION; 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.

The elevations of amylase and lipase were not associated with clinical pancreatitis in ALTA.

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

Elevations of Hepatic Enzymes
In ALTA, elevations of ALT and AST were reported in 45.5% and 64.5% 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 59.1% of patients experienced elevations of insulin.

No patients had dose reductions due to hyperglycemia or elevations of insulin.

8 DRUG INTERACTIONS

Drug-Drug Interactions

Agents that may increase brigatinib plasma concentrations

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%, $AUC_{0\text{-}INF}$ by 101% (2-fold), and $AUC_{0\text{-}120}$ by 82% (<2-fold), relative to a 90 mg brigatinib dose administered alone. (See Table 6; DOSAGE AND ADMINISTRATION, Dose Adjustment.)

The effect of moderate CYP3A inhibitors (e.g., diltiazem and verapamil) on the pharmacokinetics of brigatinib has not been studied (see Table 6).

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%, $AUC_{0\text{-}INF}$ by 12%, and $AUC_{0\text{-}120}$ by 15%, 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

CYP3A Inducers
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%, $AUC_{0\text{-}INF}$ by 80% (5-fold), and $AUC0_{\text{-}120}$ by 80% (5-fold), relative to a 180 mg brigatinib dose administered alone (see Table 6).

The effect of moderate CYP3A inducers on the pharmacokinetics of brigatinib has not been studied.

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. Clinical drug-drug interaction studies with sensitive CYP3A substrates have not been conducted. Brigatinib may reduce plasma concentrations of coadministered medications that are predominantly metabolized by CYP3A. Coadministration of ALUNBRIG™ with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of CYP3A substrates (see Table 6).

Transporter Substrates
Brigatinib is an inhibitor of P-gp, BCRP, OCT1, MATE1, and MATE2K *in vitro*. Coadministration of brigatinib with substrates of P-gp, OCT1, MATE1, and MATE2K may increase their plasma concentrations (see Table 6).

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 6; WARNINGS AND PRECAUTIONS, Cardiovascular & Monitoring and Laboratory Tests; ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology.)

Table 6 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 $AUC_{0\text{-}INF}$ 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 $AUC_{0\text{-}INF}$ by 80% (5-fold).	The concomitant use of strong CYP3A inducers with ALUNBRIG™ should be avoided.

Common name	Source of Evidence	Effect	Clinical comment
Moderate CYP3A inhibitors (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil)	T	The effect of moderate CYP3A inhibitors on the pharmacokinetics of brigatinib has not been studied.	Moderate CYP3A inhibitors may increase plasma concentrations of brigatinib. Patients should be closely monitored when ALUNBRIG™ is coadministered with moderate CYP3A inhibitors.
Moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin)	T	The effect of moderate CYP3A inducers on the pharmacokinetics of brigatinib has not been studied.	Moderate CYP3A inducers may decrease plasma concentrations of brigatinib. The concomitant use of moderate CYP3A inducers with ALUNBRIG™ should be avoided.
Pharmacokinetic Interactions (Drugs for which the exposure may be affected by brigatinib)			
Substrates of CYP3A (e.g., simvastatin, cyclosporine, cisapride, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus, quetiapine)	T	The effect of brigatinib on the pharmacokinetics of CYP3A substrates has not been studied.	Brigatinib induces CYP3A *in vitro* and 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 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™.
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.

CT = Clinical Trial; T = Theoretical

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.

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 DRUG-DRUG INTERACTIONS.)

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle 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™.

NOC/c

9 ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Brigatinib is a tyrosine kinase inhibitor that targets ALK, ROS1, and insulin-like growth factor 1 receptor (IGF-1R). Among these, brigatinib is most active against ALK. 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. No ALK mutations associated with resistance to brigatinib were observed. 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.

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 WARNINGS AND PRECAUTIONS, Cardiovascular; DRUG INTERACTIONS, Agents that decrease heart rate.)

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 153 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 13 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

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

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.

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

Race: Population pharmacokinetic analyses showed that race had no clinically meaningful effect on the pharmacokinetics of brigatinib.

Body Weight: Population pharmacokinetic analyses showed that body weight was a statistically significant covariate on brigatinib pharmacokinetics. However, there was no clinically meaningful effect of body weight on the safety and efficacy of brigatinib. Patients less than 50 kg or greater than 100 kg should be closely monitored.

Hepatic Insufficiency: As hepatic elimination is a major route of excretion for brigatinib, hepatic impairment may result in increased plasma brigatinib concentrations. The pharmacokinetics of brigatinib was similar in patients with normal hepatic function and in patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1-1.5 x ULN and any AST) based on the results of population pharmacokinetic analyses. Available data do not indicate a clinically meaningful effect of mild hepatic impairment on the safety and efficacy of ALUNBRIG™. The pharmacokinetics of brigatinib has not been studied in patients with moderate or severe hepatic impairment. (See DOSAGE AND ADMINISTRATION; WARNINGS AND PRECAUTIONS, Special Populations.)

Renal Insufficiency: The pharmacokinetics of brigatinib was similar in patients with normal renal function and in patients with mild or moderate renal impairment (creatinine clearance ≥ 30 mL/min) based on the results of population pharmacokinetic analyses. Available data do not indicate a clinically meaningful effect of mild or moderate renal impairment on the safety and efficacy of ALUNBRIG™. The pharmacokinetics of brigatinib has not been studied in patients with severe renal impairment. (See DOSAGE AND ADMINISTRATION; WARNINGS AND PRECAUTIONS, Special Populations.)

10 STORAGE, STABILITY AND DISPOSAL

Store between 15-30˚C

Keep in a safe place out of the reach of and sight of children.

PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

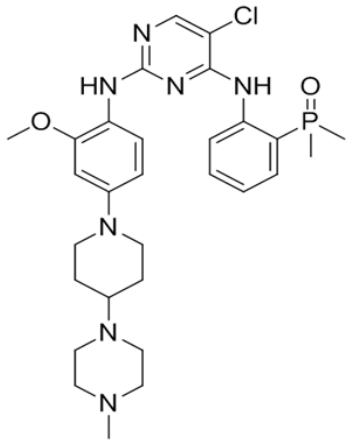
Drug Substance

Proper/Common 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: $C_{29}H_{39}ClN_7O_2P$ 584.10 g/mol

Structural formula: brigatinib



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. at pH of approximately 2.4, aqueous solubility is >300 mg/mL, and at pH of approximately 7.2, aqueous solubility is 11 mg/mL). Brigatinib does not contain any chiral centers.

NOC/c

12 CLINICAL TRIALS

Trial Design and Study Demographics

The safety and efficacy of brigatinib was evaluated in an open-label, ongoing multicenter trial (ALTA) 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 7). 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.

Investigator-assessed and Independent Review Committee (IRC) assessed systemic efficacy results from ALTA analysis are summarized in Table 8.

Table 7 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)
Adenosquamous	1 (0.9)	0 (0.0)	1 (0.5)
Muciepidermoid	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)

Study Results

Table 8 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%
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 9.

Table 9 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 (Study 1), 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 DOSAGE AND ADMINISTRATION.)

13 NON-CLINICAL 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.

Mutagenicity
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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrALUNBRIG™
Brigatinib Tablets

Read this carefully before you start taking ALUNBRIG™ (brigatinib) 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™.

What is ALUNBRIG™ used for?

ALUNBRIG™ is used to treat a type of lung cancer called non-small cell lung cancer (NSCLC). It is used when this cancer has spread to other parts of the body (metastatic). It is only used in patients whose cancer has gotten worse after taking crizotinib or in patients who are unable to take crizotinib.

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.

Please refer to the NOC/c summary box below for additional details.

"For the following indications, ALUNBRIG™ has been approved *with conditions* (NOC/c):

- ALUNBRIG™ is used to treat a type of lung cancer called non-small cell lung cancer (NSCLC). It is used when this cancer has spread to other parts of the body (metastatic). It is only used in patients whose cancer has gotten worse after taking crizotinib or in patients who are unable to take crizotinib.
- ALUNBRIG™ should only be used by people whose cancer is caused by a change in a gene called anaplastic lymphoma kinase (ALK).

This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional."

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an

NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

Serious Warnings and Precautions

ALUNBRIG™ can cause severe side effects which include:

- **Interstitial Lung Disease or Pneumonitis.** These are serious lung issues 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™ has not been studied in patients with moderate to severe hepatic impairment (liver problems).

ALUNBRIG™ has not been studied in patients with severe renal impairment (kidney problems).

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

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 ingredient: 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 you get any of these symptoms during treatment with ALUNBRIG™:
- If you experience new or worsening symptoms such as 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.
- If you experience slowing of your heart rate, or if you feel dizzy, lightheaded, or faint during treatment.
- If you become very thirsty or urinate frequently because these may be signs of a high level of sugar in the blood.
- If you experience new or worsening signs and symptoms of muscle problems. These include unexplained muscle pain or muscle pain that does not go away, tenderness or weakness.

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™ may reduce fertility in men.

Your doctor may need to change, temporarily stop or completely stop your treatment with ALUNBRIG™.

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, mibefradil, 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.

- Your doctor may lower your dose, stop your treatment for a short time, or stop treatment completely if you feel unwell.

Overdose:

If you think you have taken too much ALUNBRIG™, contact your 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 feel when taking ALUNBRIG™. If you experience any side effects not listed here, contact your healthcare professional.

Side effects of ALUNBRIG™ may include:

- Abdominal pain, also called abdominal discomfort, nausea, vomiting, diarrhea, constipation
- Dry mouth
- Inflammation of the mouth and lips
- Indigestion (*dyspepsia*)
- Rash
- Dry skin
- Itchy Skin (*pruritus*)
- Joint pain (*arthralgia*)
- Muscle pain (*myalgia*)
- Muscle spasms
- Chest pain
- Pain in arms and legs
- Fatigue
- Swelling caused by excess fluid (*edema*)
- Cough
- Headache
- Dizziness
- Trouble sleeping (*insomnia*)
- Taste disturbance (*dysgeusia*)
- Decreased appetite
- Skin sensitivity to the sun (*photosensitivity)*
- Fever
- Numbness and tingling in the hands and feet (*peripheral neuropathy*)
- Abnormal results of blood tests to check liver function

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			
High blood pressure (hypertension): 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 level of creatine phosphokinase: unexplained muscle pain, tenderness or weakness		√	
Increased blood sugar		√	

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	
(hyperglycemia): frequent urination, thirst, and hunger			
Serious Lung problems: new or worsening difficulty breathing, chest pain, shortness of breath, cough with or without mucous, or fever			√
Vision Problems: loss or change in vision		√	
Decrease in number of red blood cells (anemia): dizziness, feeling tired and weak, loss of energy, shortness of breath		√	
Decrease in number of white blood cells (neutropenia): aches, feeling tired, fever, flu-like symptoms, infections		√	
Decrease in number of lymphocytes (lymphopenia): infections		√	
Pyrexia: fever		√	
Nausea		√	
Vomiting		√	
Diarrhea: loose or watery and frequent stools		√	
COMMON			
Slow heartbeat (bradycardia): 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, talk to 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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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; the manufacturer's website http://www.takeda.com/en-ca, or by calling 1-866-295-4636.

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

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