ALUNBRIG- brigatinib tablet, film coated
ALUNBRIG- brigatinib
Takeda Pharmaceuticals America, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ALUNBRIG safely and effectively. See full prescribing information for ALUNBRIG.

ALUNBRIG® (brigatinib) tablets, for oral use
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

ALUNBRIG is a kinase inhibitor indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test. (1, 2.1)

DOSAGE AND ADMINISTRATION

90 mg orally once daily for the first 7 days; then increase to 180 mg orally once daily. May be taken with or without food. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 180 mg, 90 mg, or 30 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Interstitial Lung Disease (ILD)/Pneumonitis: Monitor for new or worsening respiratory symptoms, particularly during the first week of treatment. Withhold ALUNBRIG for new or worsening respiratory symptoms and promptly evaluate for ILD/pneumonitis. Upon recovery, either dose reduce or permanently discontinue ALUNBRIG. (2.3, 5.1)
- Hypertension: Monitor blood pressure after 2 weeks and then at least monthly during treatment. For severe hypertension, withhold ALUNBRIG, then dose reduce or permanently discontinue. (2.3, 5.2)
- Bradycardia: Monitor heart rate and blood pressure regularly during treatment. If symptomatic, withhold ALUNBRIG, then dose reduce or permanently discontinue. (2.3, 5.3)
- Visual Disturbance: Advise patients to report visual symptoms. Withhold ALUNBRIG and obtain ophthalmologic evaluation, then dose reduce or permanently discontinue ALUNBRIG. (2.3, 5.4)
- Creatine Phosphokinase (CPK) Elevation: Monitor CPK levels regularly during treatment. Based on the severity and with muscle pain or weakness, withhold ALUNBRIG, then resume or reduce dose. (2.3, 5.5)
- Pancreatic Enzymes Elevation: Monitor lipase and amylase levels regularly during treatment. Based on the severity, withhold ALUNBRIG, then resume or reduce dose. (2.3, 5.6)
- Hepatotoxicity: Monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin levels regularly during treatment. Based on severity, withhold dose, then resume at lower level. (2.3, 5.7)
- Hyperglycemia: Assess fasting serum glucose prior to starting ALUNBRIG and regularly during treatment. If not adequately controlled with optimal medical management, withhold ALUNBRIG, then consider dose reduction or permanently discontinue, based on severity. (2.3, 5.8)
- Photosensitivity: Advise patients to limit sun exposure. Based on severity withhold ALUNBRIG, then resume at the same dose, reduce the dose, or permanently discontinue. (2.3, 5.9)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.10, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (≥25%) with ALUNBRIG were diarrhea, fatigue, nausea, rash, cough, myalgia, headache, hypertension, vomiting, and dyspnea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-844-217-6468 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP3A Inhibitors: Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inhibitors. If coadministration of a strong or moderate CYP3A inhibitor is unavoidable, reduce the dose of ALUNBRIG. (2.4, 7.1)

- CYP3A Inducers: Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inducers. If coadministration of a moderate CYP3A inducer is unavoidable, increase the dose of ALUNBRIG. (2.5, 7.1)

USE IN SPECIFIC POPULATIONS

- Hepatic Impairment: Reduce the dose of ALUNBRIG for patients with severe hepatic impairment. (2.6, 8.6)
- Renal Impairment: Reduce the dose of ALUNBRIG for patients with severe renal impairment. (2.7, 8.7)
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ALUNBRIG is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of metastatic NSCLC with ALUNBRIG based on the presence of ALK positivity in tumor specimens *[see Clinical Studies (14)]*.

Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage

The recommended dosage for ALUNBRIG is:

- 90 mg orally once daily for the first 7 days; then increase the dose to 180 mg orally once daily.

Administer ALUNBRIG until disease progression or unacceptable toxicity.

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

ALUNBRIG may be taken with or without food. Instruct patients to swallow tablets whole. Do not crush or chew tablets.

If a dose of ALUNBRIG is missed or vomiting occurs after taking a dose, do not administer an additional dose and take the next dose of ALUNBRIG at the scheduled time.

2.3 Dosage Modifications for Adverse Reactions

ALUNBRIG dosage reductions for adverse reactions are summarized in Table 1.

Table 1: Recommended ALUNBRIG Dosage Reductions

Dosage	Dosage Reduction		
	First	Second	Third
90 mg once daily	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

Once reduced for adverse reactions, do not subsequently increase the dosage of ALUNBRIG. Permanently discontinue ALUNBRIG if patients are unable to tolerate the 60 mg once daily dose.

Recommendations for dosage modifications of ALUNBRIG for the management of adverse reactions are provided in Table 2.

Table 2: Recommended ALUNBRIG Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modifications
Interstitial Lung Disease (ILD) /Pneumonitis *[see Warnings and Precautions (5.1)]*	Grade 1	• If new pulmonary symptoms occur 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 new pulmonary symptoms occur 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.
		• If new pulmonary symptoms occur 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

	Grade 2	ILD/pneumonitis is suspected. • If new pulmonary symptoms occur 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 for ILD/pneumonitis.
Hypertension *[see Warnings and Precautions (5.2)]*	Grade 3 hypertension (SBP greater than or equal to 160 mmHg or DBP greater than or equal to 100 mmHg, medical intervention indicated, more than one antihypertensive drug, or more intensive therapy than previously used indicated)	• Withhold ALUNBRIG until hypertension has recovered to Grade 1 or less (SBP less than 140 mmHg and DBP less than 90 mmHg), then resume ALUNBRIG at the same dose. • Recurrence: withhold ALUNBRIG until recovery to Grade 1 or less, 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 or less, and resume at next lower dose (Table 1) or permanently discontinue treatment. • Recurrence: permanently discontinue ALUNBRIG for recurrence of Grade 4 hypertension.
		• 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

Bradycardia (HR less than 60 bpm) *[see Warnings and Precautions (5.3)]*	Symptomatic bradycardia	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 *[see Warnings and Precautions (5.4)]*	Grade 2 or 3 visual disturbance	Withhold ALUNBRIG until recovery to Grade 1 or baseline, then resume at the next lower dose (Table 1).
	Grade 4 visual disturbance	Permanently discontinue ALUNBRIG.
Creatine Phosphokinase (CPK) Elevation *[see Warnings and Precautions (5.5)]*	Grade 3 or 4 CPK elevation (greater than 5× ULN) with Grade 2 or higher muscle pain or weakness	• Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to 2.5× ULN) CPK elevation or to baseline, then resume ALUNBRIG at same dose. • Recurrence: Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to 2.5× ULN) CPK elevation or to baseline, then

		resume ALUNBRIG at the next lower dose (Table 1).
Lipase/Amylase Elevation *[see Warnings and Precautions (5.6)]*	Grade 3 lipase or amylase elevation (greater than 2× ULN)	• Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to 1.5× ULN) or to baseline, then resume ALUNBRIG at same dose. • Recurrence: Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to 1.5× ULN) or to baseline, then resume ALUNBRIG at next lower dose (Table 1).
	Grade 4 lipase or amylase elevation (greater than 5× ULN)	Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to 1.5× ULN) or to baseline, then resume ALUNBRIG at next lower dose (Table 1).
Hepatotoxicity (Elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST)) *[see Warnings and Precautions (5.7)]*	Grade 3 or 4 elevation (greater than 5 × ULN) of either ALT or AST with bilirubin less than or equal to 2 × ULN	Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to 3× ULN) or to baseline, then resume ALUNBRIG at next lower dose (Table 1).
	Grade 2 to 4 elevation (greater than 3 × ULN) of ALT or AST with concurrent total bilirubin elevation greater than 2 × ULN in the absence of cholestasis or hemolysis	Permanently discontinue ALUNBRIG.
Hyperglycemia *[see Warnings and Precautions (5.8)]*	Grade 3 (greater than 250 mg/dL or 13.9 mmol/L) or 4	If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and resume at the next lower dose (Table 1) or permanently discontinue ALUNBRIG.
	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 discontinue

Other		ALUNBRIG (Table 1).
	Grade 4	• Withhold ALUNBRIG until recovery to baseline and resume at next lower dose (Table 1). • Recurrence: Permanently discontinue ALUNBRIG.

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).

2.4 Dosage Modifications for Strong or Moderate CYP3A Inhibitors

Avoid coadministration of strong or moderate CYP3A inhibitors during treatment with ALUNBRIG *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*. If coadministration of a strong CYP3A inhibitor cannot be avoided, reduce the ALUNBRIG once daily dose by approximately 50% (i.e., from 180 mg to 90 mg, or from 90 mg to 60 mg). If coadministration of a moderate CYP3A inhibitor cannot be avoided, reduce the ALUNBRIG once daily dose by approximately 40% (i.e., 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, resume the ALUNBRIG dose that was tolerated prior to initiating the CYP3A inhibitor.

2.5 Dosage Modifications for Moderate CYP3A Inducers

Avoid coadministration of moderate CYP3A inducers during treatment with ALUNBRIG *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*. If coadministration of a moderate CYP3A inducer cannot be avoided, increase the ALUNBRIG once daily dose 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, resume the ALUNBRIG dose that was tolerated prior to initiating the moderate CYP3A inducer.

2.6 Dosage Modifications for Patients with Severe Hepatic Impairment

Reduce the ALUNBRIG once daily dose by approximately 40% (i.e., 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 C) *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

2.7 Dosage Modifications for Patients with Severe Renal Impairment

Reduce the ALUNBRIG once daily dose by approximately 50% (i.e., from 180 mg to 90 mg, or from 90 mg to 60 mg) for patients with severe renal impairment [creatinine clearance (CLcr) 15 to 29 mL/min by Cockcroft-Gault] *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

- 180 mg: oval, white to off-white film-coated tablets with "U13" debossed on one side and plain on the other side
- 90 mg: oval, white to off-white film-coated tablets with "U7" debossed on one side and plain on the other side
- 30 mg: round, white to off-white film-coated tablets with "U3" debossed on one side and plain on the other side

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis have occurred with ALUNBRIG.

In Trial ALTA 1L, ILD/pneumonitis occurred in 5.1% of patients receiving ALUNBRIG. ILD/pneumonitis occurred within 8 days of initiation of ALUNBRIG in 2.9% of patients, with Grade 3 to 4 reactions occurring in 2.2% of patients.

In Trial ALTA, ILD/pneumonitis occurred in 3.7% of patients in the 90 mg group (90 mg once daily) and 9.1% of patients in the 90→180 mg group (180 mg once daily with 7-day lead-in at 90 mg once daily). Adverse reactions consistent with possible ILD/pneumonitis occurred within 9 days of initiation of ALUNBRIG (median onset was 2 days) in 6.4% of patients, with Grade 3 to 4 reactions occurring in 2.7%.

Monitor for new or worsening respiratory symptoms (e.g., dyspnea, cough, etc.), particularly during the first week of initiating ALUNBRIG. Withhold ALUNBRIG in any patient with new or worsening respiratory symptoms, and promptly evaluate for ILD/pneumonitis or other causes of respiratory symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). For Grade 1 or 2 ILD/pneumonitis, either resume ALUNBRIG with dose reduction according to Table 1 after recovery to baseline or permanently discontinue ALUNBRIG. Permanently discontinue ALUNBRIG for Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.2 Hypertension

In ALTA 1L, hypertension was reported in 32% of patients receiving ALUNBRIG; Grade 3 hypertension occurred in 13% of patients.

In ALTA, hypertension was reported in 11% of patients in the 90 mg group who received ALUNBRIG and 21% of patients in the 90→180 mg group. Grade 3 hypertension occurred in 5.9% of patients overall.

Control blood pressure prior to treatment with ALUNBRIG. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 hypertension despite optimal antihypertensive therapy. Upon

resolution or improvement to Grade 1, resume ALUNBRIG at the same dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or recurrence of Grade 3 hypertension *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia *[see Warnings and Precautions (5.3)]*.

5.3 Bradycardia

In ALTA 1L, heart rates less than 50 beats per minute (bpm) occurred in 8.1% of patients receiving ALUNBRIG. Grade 3 bradycardia occurred in 1 patient (0.7%).

In ALTA, heart rates less than 50 beats per minute (bpm) occurred in 5.7% of patients in the 90 mg group and 7.6% of patients in the 90→180 mg group. Grade 2 bradycardia occurred in 1 (0.9%) patient in the 90 mg group.

Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drug known to cause bradycardia cannot be avoided *[see Warnings and Precautions (5.2)]*.

For symptomatic bradycardia, withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia; otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified *[see Dosage and Administration (2.3)]*.

5.4 Visual Disturbance

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 7.3% of patients receiving ALUNBRIG in the 90 mg group and 10% of patients in the 90→180 mg group. Grade 3 macular edema and cataract occurred in 1 patient each in the 90→180 mg group.

Advise patients to report any visual symptoms. 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. Permanently discontinue treatment with ALUNBRIG for Grade 4 visual disturbances *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.5 Creatine Phosphokinase (CPK) Elevation

In ALTA 1L, creatine phosphokinase (CPK) elevation occurred in 81% of patients who received ALUNBRIG. The incidence of Grade 3 or 4 CPK elevation was 24%. Dose reduction for CPK elevation occurred in 15% of patients.

In ALTA, CPK elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90 mg→180 mg group. The incidence of Grade 3 to 4

CPK elevation was 2.8% in the 90 mg group and 12% in the 90→180 mg group.

Dose reduction for CPK elevation occurred in 1.8% of patients in the 90 mg group and 4.5% in the 90→180 mg group.

Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels 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 2 *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.6 Pancreatic Enzymes Elevation

In ALTA 1L, amylase elevation occurred in 52% of patients and Grade 3 or 4 amylase elevation occurred in 6.8% of patients. Lipase elevations occurred in 59% of patients and Grade 3 or 4 lipase elevation occurred in 17% of patients.

In ALTA, amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90→180 mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 45% of patients in the 90→180 mg group. Grade 3 or 4 amylase elevation occurred in 3.7% of patients in the 90 mg group and 2.7% of patients in the 90→180 mg group. Grade 3 or 4 lipase elevation occurred in 4.6% of patients in the 90 mg group and 5.5% of patients in the 90→180 mg group.

Monitor lipase and amylase during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 or 4 pancreatic enzyme elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose as described in Table 2 *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.7 Hepatotoxicity

In ALTA 1L, aspartate aminotransferase (AST) elevations occurred in 72% of patients and Grade 3 or 4 AST elevations occurred in 4.5% of patients. Alanine aminotransferase (ALT) elevations occurred in 52% of patients and Grade 3 or 4 ALT elevations occurred in 5.2% of patients. One patient (0.7%) had a serious adverse reaction of hepatocellular injury.

In ALTA, AST elevations occurred in 38% of patients in the 90 mg group and 65% of patients in the 90→180 mg group. ALT elevations occurred in 34% of patients in the 90 mg group and 40% of patients in the 90→180 mg group. Grade 3 or 4 AST elevations occurred in 0.9% of patients in the 90 mg group and did not occur in any patients in the 90→180 mg group. Grade 3 or 4 ALT elevations did not occur in any patients in the 90 mg group and in 2.7% of patients in the 90→180 mg group.

Monitor AST, ALT and total bilirubin during treatment with ALUNBRIG, especially during first 3 months. Withhold ALUNBRIG for Grade 3 or 4 hepatic enzyme elevation with bilirubin less than or equal to 2 × ULN. Upon resolution or recovery to Grade 1 or less (less than or equal to 3 × ULN) or to baseline, resume ALUNBRIG at a next lower dose as described in Table 2. Permanently discontinue ALUNBRIG for Grade 2 to 4 hepatic enzyme elevation with concurrent total bilirubin elevation greater than 2 times the ULN in the absence of cholestasis or hemolysis *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.8 Hyperglycemia

In ALTA 1L, 56% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 7.5% of patients.

In ALTA, 43% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 3.7% of patients. Two of 20 (10%) patients with diabetes or glucose intolerance at baseline required initiation of insulin while receiving ALUNBRIG.

Assess fasting serum glucose prior to initiation of ALUNBRIG and monitor periodically thereafter. Initiate or optimize antihyperglycemic medications as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reducing the dose of ALUNBRIG as described in Table 1 or permanently discontinuing ALUNBRIG *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.9 Photosensitivity

In ALTA 1L, photosensitivity occurred in 3.7% of patients who received ALUNBRIG, with 0.7% Grade 3 to 4.

In ALTA, 0.9% of patients who received ALUNBRIG in the 90 mg group experienced photosensitivity and 0.9% of patients in the 90 mg→180 mg group. Grade 3 to 4 photosensitivity was not reported in patients in the 90 mg group or in the 90→180 mg group.

Advise patients to limit sun exposure while taking brigatinib, and for at least 5 days after discontinuation of treatment. Advise patients, when outdoors to wear a hat and protective clothing, and use a broad-spectrum Ultraviolet A (UVA)/ Ultraviolet B (UVB) sunscreen and lip balm (SPF ≥30) to help protect against sunburn. Based on the severity withhold ALUNBRIG, then resume at the same dose, or reduce the dose, or permanently discontinue as described in Table 2 *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.10 Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to pregnant women. There are no clinical data on the use of ALUNBRIG in pregnant women. Administration of brigatinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily), as well as increased post-implantation loss, malformations, and decreased fetal body weight at doses of 25 mg/kg/day (approximately 1.26 times the human exposure at 180 mg once daily) or higher.

Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Interstitial Lung Disease (ILD)/Pneumonitis *[see Warnings and Precautions (5.1)]*
- Hypertension *[see Warnings and Precautions (5.2)]*
- Bradycardia *[see Warnings and Precautions (5.3)]*
- Visual Disturbance *[see Warnings and Precautions (5.4)]*
- Creatine Phosphokinase (CPK) Elevation *[see Warnings and Precautions (5.5)]*
- Pancreatic Enzymes Elevation *[see Warnings and Precautions (5.6)]*
- Hepatotoxicity *[see Warnings and Precautions (5.7)]*
- Hyperglycemia *[see Warnings and Precautions (5.8)]*
- Photosensitivity *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Advanced ALK-positive NSCLC Without Prior ALK-targeted Therapy

In ALTA 1L, the safety of ALUNBRIG was evaluated in 136 patients with advanced ALK-positive NSCLC who had not previously received an ALK-targeted therapy *[see Clinical Studies (14)]*. The median duration of treatment with ALUNBRIG when administered as 90 mg orally once daily for the first 7 days; then increased to 180 mg orally once daily, was 24.3 months. 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 study population (N = 275) characteristics were: median age 59 years (range: 27 to 89), age less than 65 years (68%), female (55%), White (59%), Asian (39%), Stage IV disease (93%), NSCLC adenocarcinoma histology (96%), never smoker (58%), ECOG Performance Status (PS) 0 or 1 (95%), and CNS metastases at baseline (30%) *[see Clinical Studies (14)]*.

Serious adverse reactions occurred in 33% of patients receiving ALUNBRIG. The most common serious adverse reactions were pneumonia (4.4%), ILD/pneumonitis (3.7%), pyrexia (2.9%), dyspnea (2.2%), pulmonary embolism (2.2%), and asthenia (2.2%). Fatal adverse reactions occurred in 2.9% of patients and included pneumonia (1.5%), cerebrovascular accident (0.7%), and multiple organ dysfunction syndrome (0.7%).

In ALTA 1L, 13% of patients receiving ALUNBRIG permanently discontinued ALUNBRIG for adverse reactions. The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis (3.7%) and pneumonia (2.2%).

In ALTA 1L, 38% of patients required a dose reduction due to adverse reactions. The most common adverse reaction that led to dose reduction was increased creatine phosphokinase (15%), increased lipase (6.6%), increased amylase (4.4%), increased aspartate aminotransferase (2.2%), ILD/pneumonitis (2.2%) and hypertension (2.2%).

Table 3 and Table 4 summarize the common adverse reactions and laboratory

abnormalities observed in ALTA 1L.

Table 3: Adverse Reactions in ≥10% (All Grades*) or ≥2% (Grades 3-4) of Patients by Arm in ALTA 1L (N = 273)

Adverse Reactions	ALUNBRIG N = 136		Crizotinib N = 137	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Diarrhea	53	2.2	57	2.9
Nausea	30	2.2	58	2.9
Abdominal pain†	24	0.7	33	3.6
Vomiting	21	0.7	44	2.2
Constipation	18	0	42	0
Stomatitis‡	13	0.7	8.8	0
Dyspepsia	8	0	16	0.7
Gastroesophageal reflux disease	0.7	0	11	0
Skin and Subcutaneous Tissue Disorders				
Rash§	40	2.9	17	0
Pruritus¶	20	0.7	5.8	0.7
Respiratory, Thoracic and Mediastinal Disorders				
Cough	35	0	20	0
Dyspnea#	25	2.9	22Þ	3.6
ILD/Pneumonitis	5.1	2.9	2.2	0.7
Pulmonary embolism	2.2	2.2	5.8Þ	2.9
Vascular Disorders				
Hypertensionß	32	13	8	2.9
General Disorders and Administration Site Conditions				
Fatigueà	32	1.5	40	2.2
Edemaè	18	0.7	48	0.7
Pyrexia	15	0.7	15	0
Musculoskeletal and Connective Tissue Disorders				
Myalgiað	28	0	23	0
Back pain	21	0.7	17	1.5
Arthralgia	14	0	12	0
Pain in extremity	5.1	0	15	0.7
Nervous System Disorders				
Headacheø	22	2.2	17	0
Dizziness	15	0.7	20	0.7
Peripheral neuropathyý	11	0.7	18	0
Dysgeusia	2.9	0	14	0
Investigations				
Increased Blood cholesterol£	13	0	0.7	0

Cardiac Disorders				
Bradycardia¥	12	0.7	23	0
Infections and Infestations				
PneumoniaŒ	15Þ	5.1	6.6Þ	2.9
Upper respiratory tract infectionœ	12	0	10	0
Nasopharyngitis	8	0	11	0
Urinary tract infection	5.9	0.7	8.8	2.2
Metabolism and Nutrition Disorders				
Decreased Appetite	8.8	0.7	19	2.9
Eye Disorders				
Visual DisturbanceÐ	7.4	0	53	0.7

* Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03
† Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, and epigastric discomfort
‡ Includes aphthous ulcer, mouth ulceration, oral mucosal blistering and stomatitis
§ Includes dermatitis, dermatitis acneiform, dermatitis bullous, dermatitis contact, drug eruption, erythema, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic skin eruption, urticaria
¶ Included pruritus, allergic pruritus, and generalized pruritus
# Include dyspnea and exertional dyspnea
Þ Includes Grade 5 events
ß Includes hypertension and systolic hypertension
à Includes asthenia and fatigue
è Includes angioedema, eye swelling, eyelid edema, face edema, generalized edema, lip swelling, peripheral edema, periorbital edema, peripheral swelling, skin swelling, swelling and swelling face
ð Includes muscle spasms, muscle twitching, musculoskeletal discomfort, musculoskeletal pain, and myalgia
ø Includes headache and migraine
ý Includes burning sensation, dysesthesia, hyperesthesia, hypoesthesia, neuralgia, peripheral neuropathy, paraesthesia, peripheral sensory neuropathy and polyneuropathy
£ Includes blood cholesterol increased, hypercholesterolaemia
¥ Includes bradycardia, heart rate decreased, sinus bradycardia
ŒIncludes lower respiratory tract infection, lung infection, pneumonia, aspiration pneumonia, and cryptococcal pneumonia
œIncludes upper respiratory tract infection and viral upper respiratory tract infection
Ð Includes cataract, glaucoma, hypermetropia, night blindness, papilloedema, photophobia, photopsia, blurred vision, reduced visual acuity, visual field defect, visual impairment, and vitreous floaters

Table 4: Laboratory Abnormalities in ≥20% (All Grades*) of Patients by Arm in ALTA 1L (N = 273)

	ALUNBRIG N = 136†		**Crizotinib N = 137†**	
Laboratory Abnormality	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Chemistry				
Increased creatine	81	24	68	4.8

phosphokinase	81	24	68	4.8
Increased aspartate aminotransferase	72	4.5	70	5.2
Increased lipase	59	17	36	9.8
Hyperglycemia‡	56	7.5	37	3.7
Increased alanine aminotransferase	52	5.2	77	13
Increased amylase	52	6.8	25	3
Decreased phosphorous	41	3.7	39	6
Increased alkaline phosphatase	36	3	49	1.5
Increased creatinine	25	0	33	0
Potassium increased	24	1.5	31	3.7
Increased calcium	22	0	1.5	0
Decreased magnesium	21	0	6.9	0
Decreased albumin	15	0.8	52	3.7
Decreased calcium	15	0	67	1.5
Hematology				
Hemoglobin decreased	41	2.3	36	1.5
Lymphocyte count decreased	42	9.3	30	5.4
Neutrophil count decreased	12	0	34	6.8

* Per CTCAE version 4.03
† Denominator for each laboratory parameter may vary and is defined as the number of patients who had both, baseline and post-baseline test
‡ Elevated blood insulin was also observed in both arms

Clinically relevant adverse reactions in patients who received ALUNBRIG included photosensitivity (3.7%).

ALK-positive Advanced or Metastatic NSCLC Previously Treated with Crizotinib

The safety of ALUNBRIG was evaluated in 219 patients with locally advanced or metastatic ALK-positive NSCLC who received at least 1 dose of ALUNBRIG in ALTA after experiencing disease progression on crizotinib. Patients received ALUNBRIG 90 mg once daily continuously (90 mg group) or 90 mg once daily for 7 days followed by 180 mg once daily (90→180 mg group). The median duration of treatment was 7.5 months in the 90 mg group and 7.8 months in the 90→180 mg group. A total of 150 (68%) patients were exposed to ALUNBRIG for greater than or equal to 6 months and 42 (19%) patients were exposed for greater than or equal to 1 year.

The study population (N = 222) characteristics were: median age 54 years (range: 18 to 82), age less than 65 years (77%), female (57%), White (67%), Asian (31%), Stage IV disease (98%), NSCLC adenocarcinoma histology (97%), never or former smoker (95%), ECOG Performance Status (PS) 0 or 1 (93%), and CNS metastases at baseline (69%) *[see Clinical Studies (14)]*.

Serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90→180 mg group. The most common serious adverse reactions were pneumonia (5.5% overall, 3.7% in the 90 mg group, and 7.3% in the 90→180 mg group)

and ILD/pneumonitis (4.6% overall, 1.8% in the 90 mg group and 7.3% in the 90→180 mg group). Fatal adverse reactions occurred in 3.7% of patients and consisted of pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (1 patient each).

In ALTA, 2.8% of patients in the 90 mg group and 8.2% of patients in the 90→180 mg group permanently discontinued ALUNBRIG for adverse reactions. The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis (0.9% in the 90 mg group and 1.8% in the 90→180 mg group) and pneumonia (1.8% in the 90→180 mg group only).

In ALTA, 14% of patients required a dose reduction due to adverse reactions (7.3% in the 90 mg group and 20% in the 90→180 mg group). The most common adverse reaction that led to dose reduction was increased creatine phosphokinase for both regimens (1.8% in the 90 mg group and 4.5% in the 90→180 mg group).

Table 5 and Table 6 summarize the common adverse reactions and laboratory abnormalities observed in ALTA.

Table 5: Adverse Reactions in ≥10% (All Grades[*]) or ≥2% (Grades 3-4) of Patients by Dose Group in ALTA (N = 219)

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 (%)
Gastrointestinal Disorders				
Nausea	33	0.9	40	0.9
Diarrhea	19	0	38	0
Vomiting	24	1.8	23	0
Constipation	19	0.9	15	0
Abdominal Pain[†]	17	0	10	0
General Disorders and Administration Site Conditions				
Fatigue[‡]	29	1.8	36	0
Pyrexia	14	0	6.4	0.9
Respiratory, Thoracic and Mediastinal Disorders				
Cough	18	0	34	0
Dyspnea[§]	27	2.8	21	1.8[¶]
ILD/Pneumonitis	3.7	1.8	9.1	2.7
Hypoxia	0.9	0	2.7	2.7
Nervous System Disorders				
Headache[#]	28	0	27	0.9
Peripheral Neuropathy[Þ]	13	0.9	13	1.8
Skin and Subcutaneous Tissue Disorders				
Rash[ß]	15	1.8	24	3.6
Vascular Disorders				
Hypertension	11	5.5	21	6.4

Musculoskeletal and Connective Tissue Disorders				
Muscle Spasms	12	0	17	0
Back pain	10	1.8	15	1.8
Myalgia[à]	9.2	0	15	0.9
Arthralgia	14	0.9	14	0
Pain in extremity	11	0	3.6	0.9
Metabolism and Nutrition Disorders				
Decreased Appetite	22	0.9	15	0.9
Eye Disorders				
Visual Disturbance[è]	7.3	0	10	0.9
Infections				
Pneumonia	4.6	2.8[¶]	10	5.5[¶]
Psychiatric Disorders				
Insomnia	11	0	7.3	0

* Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
† Includes abdominal distension, abdominal pain, and epigastric discomfort
‡ Includes asthenia and fatigue
§ Includes dyspnea and exertional dyspnea
¶ Includes one Grade 5 event
# Includes headache and sinus headache
Þ Includes peripheral sensory neuropathy and paresthesia
ß Includes acneiform dermatitis, exfoliative rash, rash, pruritic rash, and pustular rash
à Includes musculoskeletal pain and myalgia
è Includes diplopia, photophobia, blurred vision, reduced visual acuity, visual impairment, vitreous floaters, visual field defect, macular edema, and vitreous detachment

Table 6: Laboratory Abnormalities in ≥20% (All Grades[*]) of Patients by Regimen in ALTA (N = 219)

	90 mg once daily N = 109		**90→180 mg once daily N = 110**	
Laboratory Abnormality	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Chemistry				
Increased aspartate aminotransferase	38	0.9	65	0
Hyperglycemia[†]	38	3.7	49	3.6
Increased creatine phosphokinase	27	2.8	48	12
Increased lipase	21	4.6	45	5.5
Increased alanine aminotransferase	34	0	40	2.7
Increased amylase	27	3.7	39	2.7
Increased alkaline phosphatase	15	0.9	29	0.9
Decreased phosphorous	15	1.8	23	3.6
Prolonged activated partial thromboplastin time	22	1.8	20	0.9
Hematology				

Anemia	23	0.9	40	0.9
Lymphopenia	19	2.8	27	4.5

* Per CTCAE version 4.0
† Elevated blood insulin was observed in both regimens

Clinically relevant adverse reactions in patients who received ALUNBRIG included photosensitivity (0.9%).

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 reactions and laboratory abnormalities were reported: white blood cell count decreased (28%), hyponatremia (20%), hypokalemia (19%), decreased platelet count (10%), dry skin (4.7%), pain (3.3%), and musculoskeletal stiffness (1.1%).

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ALUNBRIG

Strong or Moderate CYP3A Inhibitors

Coadministration of ALUNBRIG with a strong or moderate CYP3A inhibitor increased brigatinib plasma concentrations, which may increase the incidence of adverse reactions *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inhibitors. If coadministration of strong or moderate CYP3A inhibitors cannot be avoided, modify dose as recommended *[see Dosage and Administration (2.4)]*.

Strong or Moderate CYP3A Inducers

Coadministration of ALUNBRIG with a strong or moderate CYP3A inducer decreased brigatinib plasma concentrations, which may decrease the efficacy of ALUNBRIG *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inducers. If coadministration of moderate CYP3A inducers cannot be avoided, modify dose as recommended *[see Dosage and Administration (2.5)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no clinical data on the use of ALUNBRIG in pregnant women. Administration of brigatinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily) as well as increased post-implantation loss, malformations, and decreased fetal body weight at doses of 25 mg/kg/day (approximately 1.26 times the human exposure at 180 mg once daily) or greater *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in which pregnant rats were administered daily doses of brigatinib during organogenesis, dose-related skeletal (incomplete ossification, small incisors) and visceral anomalies were observed at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily). Malformations observed at 25 mg/kg/day (approximately 1.26 times the human AUC at 180 mg once daily) included anasarca (generalized subcutaneous edema), anophthalmia (absent eyes), forelimb hyperflexion, small, short and/or bent limbs, multiple fused ribs, bent scapulae, omphalocele (intestine protruding into umbilicus), and gastroschisis (intestines protruding through a defect in the abdominal wall) along with visceral findings of moderate bilateral dilatation of the lateral ventricles.

8.2 Lactation

Risk Summary

There are no data regarding the secretion of brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential for adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with ALUNBRIG and for 1 week following the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating ALUNBRIG *[see Use in Specific Populations (8.1)]*.

Contraception

ALUNBRIG can cause fetal harm *[see Use in Specific Populations (8.1)]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 4 months after the final dose.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

Based on findings in male reproductive organs in animals, ALUNBRIG may cause reduced fertility in males *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of ALUNBRIG in pediatric patients have not been established.

8.5 Geriatric Use

Of the 359 patients enrolled in the ALTA 1L ALUNBRIG arm and in ALTA, 26.7% were 65 and older and 7.5% were 75 and older. No overall differences in safety or effectiveness were observed between patients ≥65 years and younger patients.

8.6 Hepatic Impairment

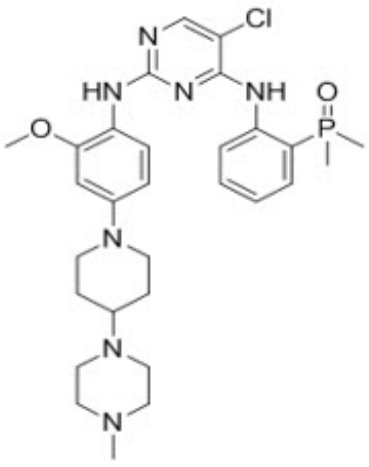
No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B). Reduce the dose of ALUNBRIG for patients with severe hepatic impairment (Child-Pugh C) *[see Dosage and Administration (2.6), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment [creatinine clearance (CLcr) 30 to 89 mL/min by Cockcroft-Gault]. Reduce the dose of ALUNBRIG for patients with severe renal impairment (CLcr 15 to 29 mL/min) *[see Dosage and Administration (2.7), Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Brigatinib is a kinase inhibitor. The chemical name for brigatinib is 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. The molecular formula is $C_{29}H_{39}ClN_7O_2P$ which corresponds to a formula weight of 584.10 g/mol. Brigatinib has no chiral centers. The chemical structure is shown below:



Brigatinib is an off-white to beige/tan solid. The pK_as 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).

ALUNBRIG is supplied for oral use as film-coated tablets containing 180 mg, 90 mg or 30 mg of brigatinib and the following inactive ingredients: lactose monohydrate,

microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate, and hydrophobic colloidal silica. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Brigatinib is a tyrosine kinase inhibitor (TKI) with *in vitro* activity at clinically achievable concentrations against multiple kinases including ALK, ROS1, insulin-like growth factor-1 receptor (IGF-1R), and FLT-3 as well as EGFR deletion and point mutations. Brigatinib inhibited autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signaling proteins STAT3, AKT, ERK1/2, and S6 in *in vitro* and *in vivo* assays. Brigatinib also 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 clinically achievable concentrations (≤500 nM), brigatinib inhibited the *in vitro* viability of cells expressing EML4-ALK and 17 mutant forms associated with resistance to ALK inhibitors including crizotinib, as well as EGFR-Del (E746-A750), ROS1-L2026M, FLT3-F691L, and FLT3-D835Y. Brigatinib exhibited *in vivo* antitumor activity against 4 mutant forms of EML4-ALK, including G1202R and L1196M mutants identified in NSCLC tumors in patients who have progressed on crizotinib. Brigatinib also reduced tumor burden and prolonged survival in mice implanted intracranially with an ALK-driven tumor cell line.

12.2 Pharmacodynamics

Brigatinib exposure-response relationships and the time course of the pharmacodynamic response are unknown.

Cardiac Electrophysiology

The QT interval prolongation potential of ALUNBRIG was assessed in 123 patients following once daily ALUNBRIG doses of 30 mg (0.16 times the recommended dose of 180 mg) to 240 mg (1.3 times the recommended dose of 180 mg). ALUNBRIG did not prolong the QT interval to a clinically relevant extent.

12.3 Pharmacokinetics

The geometric mean (CV%) steady-state maximum concentration (C_{max}) of brigatinib at ALUNBRIG doses of 90 mg and 180 mg once daily was 552 (49%) ng/mL and 1452 (60%) ng/mL, respectively, and the corresponding area under the concentration-time curve ($AUC_{0\text{-}Tau}$) was 8165 (45%) ng•h/mL and 20276 (62%) ng•h/mL. After a single dose and multiple dosing of ALUNBRIG, systemic exposure of brigatinib was dose proportional over the dose range of 60 mg (0.3 times the recommended dose of 180 mg) to 240 mg (1.3 times the recommended dose of 180 mg) once daily. The mean accumulation ratio after repeat dosing was 1.9 to 2.4.

Absorption

Following administration of single oral doses of ALUNBRIG of 30 mg to 240 mg, the median time to peak concentration (T_{max}) ranged from 1 to 4 hours.

Effect of Food

Brigatinib C_{max} was reduced by 13% with no effect on AUC in healthy subjects administered ALUNBRIG after a high fat meal (approximately 920 calories, 58 grams carbohydrate, 59 grams fat and 40 grams protein) 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 ALUNBRIG 180 mg once daily, the mean apparent volume of distribution (V_z/F) of brigatinib at steady-state was 307 L.

Elimination

Following oral administration of ALUNBRIG 180 mg once daily, the mean apparent oral clearance (CL/F) of brigatinib at steady-state is 8.9 L/h and the mean plasma elimination half-life is 25 hours.

Metabolism

Brigatinib is primarily metabolized by CYP2C8 and CYP3A4 *in vitro*. Following oral administration of a single 180 mg dose of radiolabeled brigatinib to healthy subjects, N-demethylation and cysteine conjugation were the two major metabolic pathways. Unchanged brigatinib (92%) was the major circulating radioactive component.

Excretion

Following oral administration of a single 180 mg dose of radiolabeled brigatinib to healthy 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.

Specific Populations

Age, race, sex, body weight, and albumin concentration have no clinically meaningful effect on the pharmacokinetics of brigatinib.

Patients with Hepatic Impairment

Following a single dose of ALUNBRIG 90 mg, unbound brigatinib systemic exposure ($AUC_{0\text{-}INF}$) was 37% higher in subjects with severe hepatic impairment (Child-Pugh C) compared to subjects with normal hepatic function. Unbound brigatinib systemic exposure ($AUC_{0\text{-}INF}$) was similar between subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment and subjects with normal hepatic function *[see Dosage and Administration (2.6)]*.

Patients with Renal Impairment

Following a single dose of ALUNBRIG 90 mg, unbound brigatinib systemic exposure ($AUC_{0\text{-}INF}$) was 86% higher in subjects with severe renal impairment [creatinine clearance (CLcr) 15 to 29 mL/min] compared to subjects with normal renal function.

Based on a population pharmacokinetic analysis, brigatinib exposures were similar among 125 subjects with mild renal impairment (CLcr 60 to 89 mL/min), 34 subjects with moderate renal impairment (CLcr 30 to 59 mL/min) and 270 subjects with normal renal function (CLcr ≥90 mL/min) *[see Dosage and Administration (2.7)]*.

Drug Interaction Studies

Clinical Studies

Effect of Strong and Moderate CYP3A Inhibitors on Brigatinib:

Coadministration of 200 mg twice daily doses of itraconazole (a strong CYP3A inhibitor) with a single 90 mg dose of ALUNBRIG increased brigatinib C_{max} by 21% and $AUC_{0\text{-}INF}$ by 101%, relative to a 90 mg dose of ALUNBRIG administered alone *[see Dosage and Administration (2.4), Drug Interactions (7.1)]*. A moderate CYP3A inhibitor is predicted to increase the AUC of brigatinib by approximately 40%.

Effect of Strong CYP2C8 Inhibitors on Brigatinib:

Coadministration of 600 mg twice daily doses of gemfibrozil (a strong CYP2C8 inhibitor) with a single 90 mg dose of ALUNBRIG decreased brigatinib C_{max} by 41% and $AUC_{0\text{-}INF}$ by 12%, relative to a 90 mg dose of ALUNBRIG administered alone. The effect of gemfibrozil on the pharmacokinetics of brigatinib is not clinically meaningful and the underlying mechanism for the decreased exposure of brigatinib is unknown.

Effect of Strong and Moderate CYP3A Inducers on Brigatinib:

Coadministration of 600 mg daily doses of rifampin (a strong CYP3A inducer) with a single 180 mg dose of ALUNBRIG decreased brigatinib C_{max} by 60% and $AUC_{0\text{-}INF}$ by 80%, relative to a 180 mg dose of ALUNBRIG administered alone *[see Dosage and Administration (2.5), Drug Interactions (7.1)]*. A moderate CYP3A inducer is predicted to decrease the AUC of brigatinib by approximately 50%.

Effect of Brigatinib on CYP3A Substrates:

Coadministration of 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% and $AUC_{0\text{-}INF}$ by 26%, relative to a 3 mg oral dose of midazolam administered alone. Brigatinib is considered a weak inducer of CYP3A.

In Vitro Studies

Effect of Brigatinib on CYP Enzymes:

Brigatinib, at clinically relevant plasma concentrations, induced CYP3A via activation of the pregnane X receptor (PXR). Brigatinib may also induce CYP2C enzymes via the same mechanism at clinically relevant concentrations.

Brigatinib did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 at clinically relevant concentrations.

Effect of P-glycoprotein and BCRP Inhibitors on Brigatinib:

Brigatinib is a substrate of the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Given that brigatinib exhibits high solubility and high permeability *in vitro*, P-gp and BCRP inhibitors are unlikely to increase plasma concentrations of brigatinib.

Effect of Other Transporters on Brigatinib:

Brigatinib is not a substrate of organic anion transporting polypeptide (OATP1B1, OATP1B3), organic anion transporter (OAT1, OAT3), organic cation transporter (OCT1, OCT2), multidrug and toxin extrusion protein (MATE1, MATE2K), or bile salt export pump

(BSEP).

Effect of Brigatinib on Transporters:

Brigatinib is an inhibitor of P-gp, BCRP, OCT1, MATE1, and MATE2K *in vitro*. Therefore, brigatinib may have the potential to increase concentrations of coadministered substrates of these transporters. Brigatinib at clinically relevant concentrations did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, OCT2 or BSEP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with brigatinib.

Treatment with brigatinib resulted in chromosomal damage in an *in vivo* mammalian erythrocyte micronucleus in the rat, but was not mutagenic in the Ames or *in vitro* mammalian chromosome aberration tests.

Dedicated animal fertility studies were not conducted with brigatinib. Testicular toxicity was observed in repeat-dose animal studies at doses resulting in exposure as low as 0.2 times the exposure in patients at the 180 mg dose. In rats, findings included lower weight of testes, seminal vesicles and prostate gland, and testicular tubular degeneration; these effects were not reversible during the 2 month recovery period. In monkeys, findings included reduced size of testes along with microscopic evidence of hypospermatogenesis; these effects were reversible during the recovery period.

14 CLINICAL STUDIES

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

The efficacy of ALUNBRIG was demonstrated in a randomized (1:1), open-label, multicenter trial (ALTA 1L, NCT02737501) in adult patients with advanced ALK-positive NSCLC who had not previously received an ALK-targeted therapy. The study required patients to have an ALK rearrangement based on a local standard of care testing. Eligible patients were allowed to have up to 1 prior regimen of chemotherapy in the locally advanced or metastatic setting and were required to have an 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 interstitial lung disease, drug-related pneumonitis, or radiation pneumonitis were excluded. The major efficacy outcome measure was progression-free survival (PFS) as evaluated by a Blinded Independent Review Committee (BIRC) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Additional efficacy outcome measures included confirmed overall response rate (ORR), duration of response (DOR), intracranial ORR, and intracranial DOR as evaluated by BIRC, and overall survival (OS).

A total of 275 patients were randomized to receive ALUNBRIG 180 mg orally once daily with a 7-day lead-in at 90 mg once daily (n = 137) or crizotinib 250 mg orally twice daily (n = 138). Of the 275 enrolled patients, 239 had positive results using the companion diagnostic test, the Vysis ALK Break Apart FISH Probe Kit; central results were negative for 20 patients and unavailable for 16 patients. Crossover from the crizotinib arm to the ALUNBRIG arm was permitted following disease progression.

Randomization was stratified by CNS metastases (present vs absent) and prior chemotherapy use for locally advanced or metastatic disease (yes, no).

Baseline demographic characteristics of the overall study population were: median age 59 years (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 overall study population were: 93% with Stage IV disease; 27% received chemotherapy in the locally advanced or metastatic setting; 14% had received CNS radiation; 31% had bone metastases; and 20% had liver metastases. CNS metastases were present in 35% (n = 96) of patients; 41 of those patients had measurable CNS lesions.

ALTA 1L demonstrated a statistically significant improvement in PFS by BIRC. Efficacy results from this study are described in Table 7 and Figure 1.

Table 7: Efficacy Results by BIRC Assessment in ALTA 1L

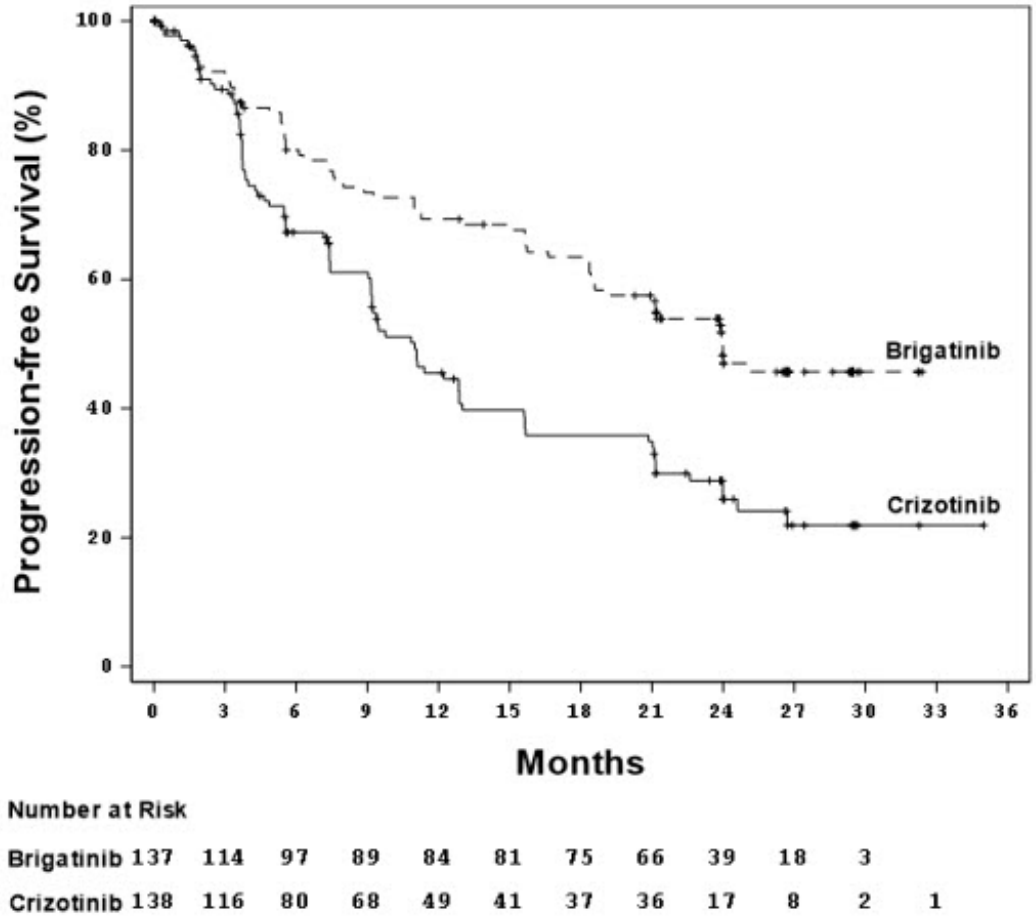
Efficacy Parameters	ALUNBRIG N = 137	Crizotinib N = 138
Progression-Free Survival		
Number of Events, n (%)	63 (46%)	87 (63%)
Median (months) (95% CI)	24.0 (18.5, NE)	11.0 (9.2, 12.9)
Hazard ratio (95% CI)	0.49 (0.35, 0.68)	
p-value*	<.0001	
Tumor Responses		
Confirmed Overall Response Rate, % (95% CI)	74% (66, 81)	62% (53, 70)
p-value*	0.0342	
Complete Response, % (95% CI)	15% (9, 22)	9% (5, 15)
Partial Response, % (95% CI)	59% (50, 67)	53% (44, 61)
Duration of Response		
Number of Confirmed responders	n=101	n=85
Median (months) (95% CI) †	33.1 (22.0, NE)	13.8 (10.4, 20.8)

CI = Confidence Interval, NE = Not Estimable

* 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

† Based on final analysis data for confirmed responders observed at interim analysis

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



At the final analysis of overall survival, conducted approximately 3 years after the last patient enrolled, there were 92 deaths (33% of all patients) including 41 deaths on the ALUNBRIG arm and 51 deaths on the crizotinib arm; median OS was not reached on either arm.

BIRC assessment of confirmed intracranial ORR and intracranial DOR according to RECIST v1.1 in the subgroup of 41 patients with measurable CNS metastases (≥10 mm in longest diameter) at baseline are summarized in Table 8. 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.

Table 8: Intracranial Overall Response in Patients with Measurable CNS Metastases in ALTA 1L

Efficacy Parameter	ALUNBRIG (N = 18)	Crizotinib (N = 23)
Confirmed Intracranial Overall Response Rate, (95% CI)	78% (52, 94)	26% (10, 48)
Complete Response, % (95% CI)	28% (10, 53)	0 (0, 15)
Partial Response, % (95% CI)	50% (26, 74)	26% (10, 48)
Duration of Intracranial Response		
Number of Confirmed	n = 14	n = 6

Responders	n = 14	n = 6
Intracranial Response Duration ≥24 months	64%	NE

CI = Confidence Interval; NE = Not Estimable

ALK-positive Advanced or Metastatic NSCLC Previously Treated with Crizotinib

The efficacy of ALUNBRIG was demonstrated in a two-arm, open-label, multicenter trial (ALTA, NCT02094573) in adult patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who had progressed on crizotinib. The study required patients to have a documented ALK rearrangement based on an FDA-approved test or a different test with adequate archival tissue to confirm ALK arrangement by the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit test. Key eligibility criteria included an ECOG Performance Status of 0-2 and progression on crizotinib. Neurologically stable patients with central nervous system (CNS) metastases were permitted to enroll. Patients with a history of interstitial lung disease or drug-related pneumonitis or who had received crizotinib within 3 days of the first dose of brigatinib were excluded. The major efficacy outcome measure was confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by an Independent Review Committee (IRC). Additional efficacy outcome measures included Investigator-assessed ORR, duration of response (DOR), intracranial ORR, and intracranial DOR.

A total of 222 patients were randomized to receive ALUNBRIG either 90 mg once daily (90 mg arm; n = 112) or 180 mg once daily following a 7-day lead-in at 90 mg once daily (90→180 mg arm; n = 110). Randomization was stratified by CNS metastases (present vs absent) and best prior response to crizotinib (complete or partial response vs any other response/unevaluable).

Baseline demographic characteristics of the overall study population were: median age 54 years (range: 18 to 82, 23% 65 and over), 67% White and 31% Asian, 57% female, 36% ECOG PS 0 and 57% ECOG PS 1, and 95% never or former smokers. The disease characteristics of the overall study population were: Stage IV disease in 98%, adenocarcinoma histology in 97%, prior systemic chemotherapy in 74%, CNS metastases in 69% (61% had received prior CNS radiation), bone metastases in 39%, and liver metastases in 26% of patients. Sixty-four percent of patients had an objective response to prior crizotinib.

The median duration of follow-up was 8 months (range: 0.1 to 20.2). Efficacy results from ALTA are summarized in Table 9.

Table 9: ALTA Efficacy Results

	IRC Assessment		**Investigator Assessment**	
Efficacy Parameter	**90 mg once daily (N = 112)**	**90→180 mg once daily (N = 110)**	**90 mg once daily (N = 112)**	**90→180 mg once daily (N = 110)**
Overall Response	48%	53%	45%	54%

Rate (95% CI)	(39,58)	(43,62)	(35,54)	(44,63)
Complete Response, n (%)	4 (3.6%)	5 (4.5%)	1 (0.9%)	4 (3.6%)
Partial Response, n (%)	50 (45%)	53 (48%)	49 (44%)	55 (50%)
Duration of Response, median in months (95% CI)	13.8 (7.4,NE)	13.8 (9.3,NE)	13.8 (5.6,13.8)	11.1 (9.2,13.8)

CI = Confidence Interval; NE = Not Estimable

IRC assessment of intracranial ORR and intracranial DOR according to RECIST v1.1 in the subgroup of 44 patients with measurable CNS metastases (≥10 mm in longest diameter) at baseline are summarized in Table 10. 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.

Table 10: Intracranial Overall Response in Patients with Measurable CNS Metastases in ALTA

	IRC Assessment	
Efficacy Parameter	**90 mg once daily (N = 26)**	**90→180 mg once daily (N = 18)**
Intracranial Overall Response Rate, (95 % CI)	42% (23,63)	67% (41,87)
Complete Response, n (%)	2 (7.7%)	0
Partial Response, n (%)	9 (35%)	12 (67%)
Duration of Intracranial Response		
Number of Responders	11	12
Intracranial Response Duration ≥6 months	7 (64%)	6 (50%)
Intracranial Response Duration ≥12 months	4 (36%)	3 (25%)

CI = Confidence Interval

16 HOW SUPPLIED/STORAGE AND HANDLING

180 mg tablets: oval, white to off-white film-coated tablets with "U13" debossed on one side and plain on the other side; available in:

Bottle of 23 tablets	NDC 63020-180-23
Bottle of 30 tablets	NDC 63020-180-30

90 mg tablets: oval, white to off-white film-coated tablets with "U7" debossed on one

side and plain on the other side; available in:

Bottle of 7 tablets	NDC 63020-090-07
Bottle of 30 tablets	NDC 63020-090-30

30 mg tablets: round, white to off-white film-coated tablets with "U3" debossed on one side and plain on the other side; available in:

Bottle of 30 tablets	NDC 63020-113-30

90 mg / 7 count tablets (NDC 63020-090-07) and 180 mg / 23 count tablets (NDC 63020-180-23) are also available in a single carton as a one-month initiation pack:

One carton containing one bottle of 90 mg tablets (7 count) and one bottle of 180 mg tablets (23 count)	NDC 63020-198-30

Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) (see USP).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the symptoms and risks of serious pulmonary adverse reactions such as ILD/pneumonitis. Advise patients to immediately report any new or worsening respiratory symptoms *[see Warnings and Precautions (5.1)]*.

Hypertension

Advise patients of risks of hypertension and to promptly report signs or symptoms of hypertension *[see Warnings and Precautions (5.2)]*.

Bradycardia

Advise patients to report any symptoms of bradycardia and to inform their healthcare provider about the use of heart and blood pressure medications *[see Warnings and Precautions (5.3)]*.

Visual Disturbance

Advise patients to inform their healthcare provider of any new or worsening vision symptoms *[see Warnings and Precautions (5.4)]*.

Creatine Phosphokinase (CPK) Elevation

Inform patients of the signs and symptoms of creatine phosphokinase (CPK) elevation and the need for monitoring during treatment. Advise patients to inform their healthcare provider of any new or worsening symptoms *[see Warnings and Precautions (5.5)]*.

Pancreatic Enzymes Elevation

Inform patients of the signs and symptoms of pancreatitis and the need to monitor for amylase and lipase elevations during treatment *[see Warnings and Precautions (5.6)]*.

Hepatotoxicity

Inform patients of the signs and symptoms of hepatotoxicity, and the need to monitor for aspartate aminotransferase (AST), alanine animotransferase (ALT) and total bilirubin elevations during treatment. Advise patients to inform their healthcare provider of any new or worsening symptoms *[see Warnings and Precautions (5.7)]*.

Hyperglycemia

Inform patients of the risks of new or worsening hyperglycemia and the need to periodically monitor glucose levels. Advise patients with diabetes mellitus or glucose intolerance that antihyperglycemic medications may need to be adjusted during treatment with ALUNBRIG *[see Warnings and Precautions (5.8)]*.

Photosensitivity

Inform patients of the signs and symptoms of photosensitivity. Advise patients to limit sun exposure while taking ALUNBRIG and for at least 5 days after the final dose. Advise patients to wear a hat, protective clothing, and to use a broad-spectrum Ultraviolet A (UVA)/ Ultraviolet B (UVB) sunscreen and lip balm (SPF ≥30) to protect against sunburn *[see Warnings and Precautions (5.9)]*.

Females and Males of Reproductive Potential

Embryo-Fetal Toxicity

Advise females and males of reproductive potential that ALUNBRIG can cause fetal harm *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1)]*.

- Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy and to use effective contraception during treatment with ALUNBRIG and for at least 4 months after the final dose *[see Use in Specific Populations (8.3)]*.
- Advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise females not to breastfeed during treatment with ALUNBRIG and for at least 1 week following the final dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males of reproductive potential of the potential for reduced fertility from ALUNBRIG *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

Drug Interactions

Advise patients to inform their healthcare provider of all concomitant medications,

including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid grapefruit or grapefruit juice while taking ALUNBRIG *[see Drug Interactions (7)]*.

Dosing and Administration

Instruct patients to start with 90 mg of ALUNBRIG once daily for the first 7 days and if tolerated, increase the dose to 180 mg once daily. Advise patients to take ALUNBRIG with or without food *[see Dosage and Administration (2.2)]*.

Missed Dose

Advise patients that if a dose of ALUNBRIG is missed or if the patient vomits after taking a dose of ALUNBRIG, not to take an extra dose, but to take the next dose at the regular time *[see Dosage and Administration (2.2)]*.

Distributed by:
Takeda Pharmaceuticals America, Inc.
Cambridge, MA 02142

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ABG346 R6

PATIENT INFORMATION
ALUNBRIG® (uh-lun-brig)
(brigatinib)
tablets

What is the most important information I should know about ALUNBRIG?
ALUNBRIG can cause serious side effects, including:

- **Lung problems. ALUNBRIG may cause severe or life-threatening swelling (inflammation) of the lungs any time during treatment, and can lead to death.** These lung problems happen **especially within the first week of treatment** with ALUNBRIG. Symptoms may be similar to those symptoms from lung cancer. Tell your healthcare provider right away if you have any new or worsening symptoms, including:
  - trouble breathing or shortness of breath
  - chest pain
  - cough with or without mucus
  - fever
- **High blood pressure (hypertension).** ALUNBRIG may cause high blood pressure. Your healthcare provider will check your blood pressure before starting and during treatment with ALUNBRIG. Tell your healthcare provider right away if you get headaches, dizziness, blurred vision, chest pain or shortness of breath.
- **Slow heart rate (bradycardia).** ALUNBRIG may cause very slow heartbeats that can be severe. Your healthcare provider will check your heart rate during treatment with ALUNBRIG. Tell your healthcare provider right away if you feel dizzy, lightheaded, or faint during treatment with ALUNBRIG. Tell your healthcare provider if you take any heart or blood pressure medicines.

- **Vision problems.** ALUNBRIG may cause vision problems. Your healthcare provider may stop ALUNBRIG and refer you to an eye specialist if you develop severe vision problems during treatment with ALUNBRIG. Tell your healthcare provider right away if you have any loss of vision or any change in vision, including:
  - double vision
  - seeing flashes of light
  - blurry vision
  - light hurting your eyes
  - new or increased floaters
- **Muscle pain, tenderness, and weakness (myalgia).** ALUNBRIG may increase the level of an enzyme in your blood called creatine phosphokinase (CPK), which may be a sign of muscle damage. Your healthcare provider will do blood tests to check your blood levels of CPK during treatment with ALUNBRIG. Tell your healthcare provider right away if you get new or worsening signs and symptoms of muscle problems, including unexplained muscle pain or muscle pain that does not go away, tenderness, or weakness.
- **Inflammation of the pancreas (pancreatitis).** ALUNBRIG may increase enzymes in your blood called amylase and lipase, which may be a sign of pancreatitis. Your healthcare provider will do blood tests to check your pancreatic enzyme blood levels during treatment with ALUNBRIG. Tell your healthcare provider right away if you get new or worsening signs and symptoms of pancreatitis, including upper abdominal pain that may spread to the back and get worse with eating, weight loss, or nausea.
- **Liver problems (hepatotoxicity).** ALUNBRIG may increase the levels of bilirubin in your blood and enzymes called aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in your blood, which may be a sign of liver problems. Your healthcare provider will do blood tests to check your liver during treatment with ALUNBRIG. Tell your healthcare provider right away if you get new or worsening signs or symptoms, including:
  - yellowing of your skin or the white part of your eyes
  - dark or brown (tea color) urine
  - nausea or vomiting
  - pain on the right side of your stomach area
  - bleed or bruise more easily than normal
  - itchy skin
  - decreased appetite
  - feeling tired
- **High blood sugar (hyperglycemia).** ALUNBRIG may increase your blood sugar levels. Your healthcare provider will do blood tests to check your blood sugar levels before starting and during treatment with ALUNBRIG. Your healthcare provider may need to start or change your blood sugar medicine to control your blood sugar levels. Tell your healthcare provider right away if you get new or worsening signs and symptoms of hyperglycemia, including:
  - feeling very thirsty
  - needing to urinate more than usual
  - feeling very hungry
  - feeling sick to your stomach
  - feeling weak or tired
  - feeling confused

See "What are the possible side effects of ALUNBRIG?" for information about side effects.

What is ALUNBRIG?

ALUNBRIG is a prescription medicine used to treat adults with non-small cell lung cancer (NSCLC):

- that has a certain type of abnormal anaplastic lymphoma kinase (ALK) gene, **and**
- that has spread to other parts of your body.

It is not known if ALUNBRIG is safe and effective in children.

Before you take ALUNBRIG, tell your healthcare provider about all of your medical conditions, including if you:

- have lung or breathing problems
- have high blood pressure
- have a slow heartbeat
- have any vision problems
- have or have had pancreatitis
- have liver problems
- have diabetes mellitus or glucose intolerance
- have kidney problems or are on dialysis
- are pregnant or plan to become pregnant. ALUNBRIG can harm your unborn baby. Your healthcare provider will determine whether or not you are pregnant before you start treatment with ALUNBRIG. Tell your healthcare provider right away if you become pregnant during treatment with ALUNBRIG or think you may be pregnant.
  - **Females** who are able to become pregnant should use effective birth control during treatment with ALUNBRIG and for at least 4 months after the final dose of ALUNBRIG. Talk to your healthcare provider about birth control choices that are right for you during treatment with ALUNBRIG.
  - **Males** who have female partners that are able to become pregnant should use effective birth control during treatment with ALUNBRIG and for at least 3 months after the final dose of ALUNBRIG.
- are breastfeeding or plan to breastfeed. It is not known if ALUNBRIG passes into your breast milk. Do not breastfeed during treatment with ALUNBRIG and for 1 week after the final dose of ALUNBRIG.

Tell your healthcare provider about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, or herbal supplements.

How should I take ALUNBRIG?

- Take ALUNBRIG exactly as your healthcare provider tells you to take it. Do not change your dose or stop taking ALUNBRIG unless your healthcare provider tells you to.
- Your healthcare provider will start you on a low dose (90 mg) of ALUNBRIG for the first 7 days of treatment. If you tolerate this dose of ALUNBRIG well, your healthcare provider may increase your dose after the first 7 days of treatment.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with ALUNBRIG if you develop side effects.
- Take ALUNBRIG 1 time each day.
- Take ALUNBRIG with or without food.
- Swallow ALUNBRIG tablets whole. Do not crush or chew tablets.
- If you miss a dose of ALUNBRIG, do not take the missed dose. Take your next dose at your regular time.
- If you vomit after taking a dose of ALUNBRIG, do not take an extra dose. Take your next dose at your regular time.

What should I avoid while taking ALUNBRIG?

- Limit your time in the sun during treatment with ALUNBRIG and for at least 5 days after your final dose. ALUNBRIG may make your skin sensitive to sunlight. You may burn more easily and get severe sunburns. When you are in the sun, wear a hat and protective clothing, and use a broad-spectrum sunscreen and lip balm with a Sun Protection Factor (SPF) of 30 or greater to protect against sunburn.
- Avoid eating grapefruit or drinking grapefruit juice during treatment with ALUNBRIG. Grapefruit may increase the amount of ALUNBRIG in your blood.

What are the possible side effects of ALUNBRIG?
ALUNBRIG may cause serious side effects, including:

- **See "What is the most important information I should know about ALUNBRIG?".**

The most common side effects of ALUNBRIG include:

- diarrhea
- fatigue
- nausea
- rash
- cough
- muscle pain
- headache
- high blood pressure
- vomiting
- difficulty breathing

ALUNBRIG may cause fertility problems in males. This may affect your ability to father a child. Talk to your healthcare provider if you have concerns about fertility.
These are not all of the possible side effects of ALUNBRIG.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ALUNBRIG?

- Store ALUNBRIG at room temperature between 68°F to 77°F (20°C to 25°C).

Keep ALUNBRIG and all medicines out of the reach of children.

General information about the safe and effective use of ALUNBRIG.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ALUNBRIG for a condition for which it was not prescribed. Do not give ALUNBRIG to other people, even if they have the same symptoms you have. It may harm them.
You can ask your healthcare provider or pharmacist for information about ALUNBRIG that is written for health professionals.

What are the ingredients in ALUNBRIG?
Active ingredient: brigatinib
Inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate, and hydrophobic colloidal silica. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol, and titanium dioxide.
Distributed by: **Takeda Pharmaceuticals America, Inc.**, Cambridge, MA 02142

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For more information, go to www.alunbrig.com or call 1-844-217-6468. ABG346 R6

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: October 2024

PRINCIPAL DISPLAY PANEL - 30 mg Tablet Bottle Carton

NDC 63020-113-30

ALUNBRIG®
(brigatinib) tablets

30 mg

Rx Only

30 Tablets

PRINCIPAL DISPLAY PANEL - 90 mg Tablet Bottle Carton

NDC 63020-090-30

ALUNBRIG®
(brigatinib) tablets

90 mg

Rx Only

30 Tablets

PRINCIPAL DISPLAY PANEL - 180 mg Tablet Bottle Carton

NDC 63020-180-30

ALUNBRIG®
(brigatinib) tablets

180 mg

Rx Only

30 Tablets

PRINCIPAL DISPLAY PANEL - Kit Carton

NDC 63020-198-30
INITIATION PACK

ALUNBRIG®
(brigatinib) tablets

Rx Only | Oral Use

Usual Dose: One 90 mg tablet orally once daily for the first 7 days; if tolerated, increase to one 180 mg tablet orally once daily.
See accompanying full Prescribing Information for complete details.

90 mg

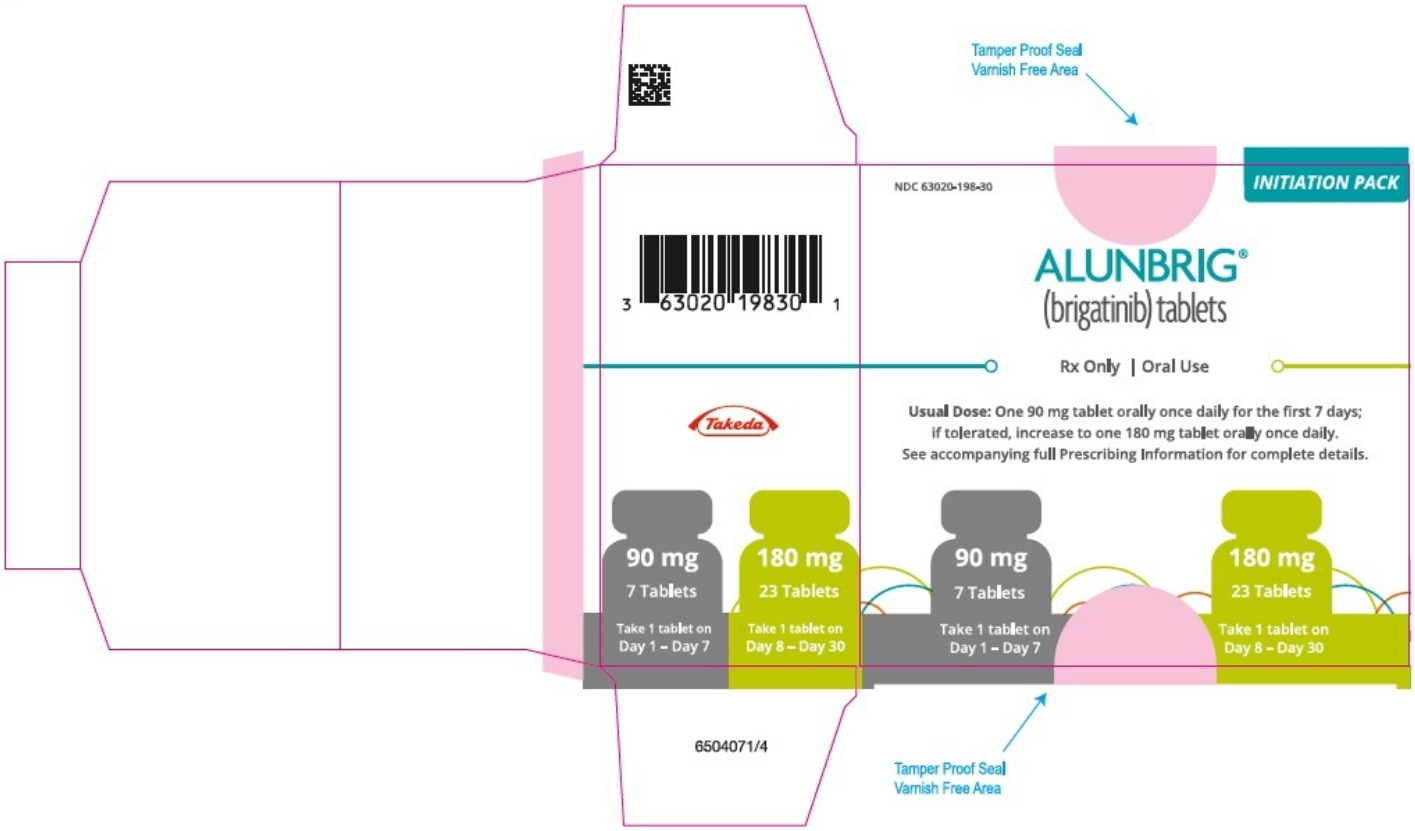
7 Tablets

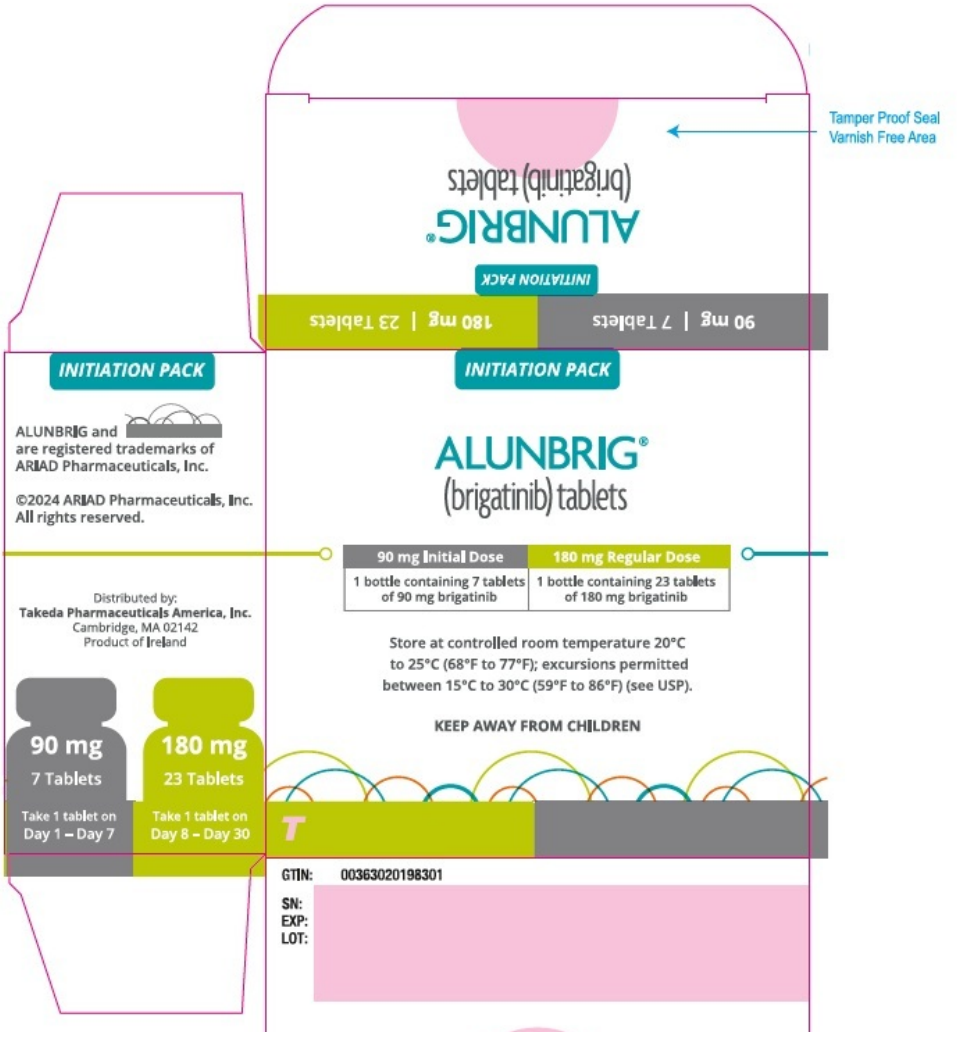
Take 1 tablet on
Day 1 - Day 7

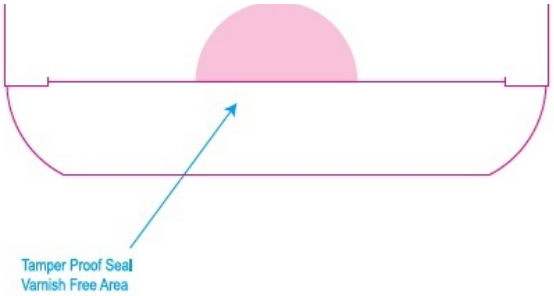
180 mg

23 Tablets

Take 1 tablet on
Day 8 - Day 30


Tamper Proof Seal
Varnish Free Area
NDC 63020-198-30
INITIATION PACK
3 63020 19830 1
ALUNBRIG®
(brigatinib) tablets
Rx Only | Oral Use
Takeda
Usual Dose: One 90 mg tablet orally once daily for the first 7 days;
if tolerated, increase to one 180 mg tablet orally once daily.
See accompanying full Prescribing Information for complete details.
90 mg
7 Tablets
Take 1 tablet on
Day 1 – Day 7
180 mg
23 Tablets
Take 1 tablet on
Day 8 – Day 30
90 mg
7 Tablets
Take 1 tablet on
Day 1 – Day 7
180 mg
23 Tablets
Take 1 tablet on
Day 8 – Day 30
6504071/4
Tamper Proof Seal
Varnish Free Area


Tamper Proof Seal
Varnish Free Area
INITIATION PACK
INITIATION PACK
ALUNBRIG®
(brigatinib) tablets
ALUNBRIG and
are registered trademarks of
ARIAD Pharmaceuticals, Inc.
©2024 ARIAD Pharmaceuticals, Inc.
All rights reserved.
90 mg Initial Dose
1 bottle containing 7 tablets of 90 mg brigatinib
180 mg Regular Dose
1 bottle containing 23 tablets of 180 mg brigatinib
Distributed by:
Takeda Pharmaceuticals America, Inc.
Cambridge, MA 02142
Product of Ireland
Store at controlled room temperature 20°C
to 25°C (68°F to 77°F); excursions permitted
between 15°C to 30°C (59°F to 86°F) (see USP).
KEEP AWAY FROM CHILDREN
90 mg
7 Tablets
Take 1 tablet on
Day 1 – Day 7
180 mg
23 Tablets
Take 1 tablet on
Day 8 – Day 30
GTIN: 00363020198301
SN:
EXP:
LOT:



ALUNBRIG

brigatinib tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63020-113
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
brigatinib (UNII: HYW8DB273J) (brigatinib - UNII:HYW8DB273J)	brigatinib	30 mg

Inactive Ingredients

Ingredient Name	Strength
Lactose monohydrate (UNII: EWQ57Q8I5X)	
Microcrystalline cellulose (UNII: OP1R32D61U)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
Magnesium stearate (UNII: 70097M6I30)	

Product Characteristics

Color	WHITE	**Score**	no score
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	U3
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63020-113-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	10/02/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208772	04/28/2017	

ALUNBRIG

brigatinib tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63020-090
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
brigatinib (UNII: HYW8DB273J) (brigatinib - UNII:HYW8DB273J)	brigatinib	90 mg

Inactive Ingredients

Ingredient Name	Strength
Lactose monohydrate (UNII: EWQ57Q8I5X)	
Microcrystalline cellulose (UNII: OP1R32D61U)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
Magnesium stearate (UNII: 70097M6I30)	

Product Characteristics

Color	WHITE	**Score**	no score
Shape	OVAL	**Size**	15mm
Flavor		**Imprint Code**	U7
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63020-090-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	10/02/2017	
2	NDC:63020-090-07	7 in 1 BOTTLE; Type 0: Not a Combination Product	10/02/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208772	04/28/2017	

ALUNBRIG

brigatinib tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63020-180
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
brigatinib (UNII: HYW8DB273J) (brigatinib - UNII:HYW8DB273J)	brigatinib	180 mg

Inactive Ingredients	
Ingredient Name	**Strength**
Lactose monohydrate (UNII: EWQ57Q8I5X)	
Microcrystalline cellulose (UNII: OP1R32D61U)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
Magnesium stearate (UNII: 70097M6I30)	

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	OVAL	**Size**	19mm
Flavor		**Imprint Code**	U13
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:63020-180-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	10/02/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208772	04/28/2017	

ALUNBRIG

brigatinib kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63020-198

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:63020-198-30	1 in 1 CARTON	10/02/2017	

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1 BOTTLE	7
Part 2	1 BOTTLE	23

Part 1 of 2

ALUNBRIG

brigatinib tablet, film coated

Product Information	
Item Code (Source)	NDC:63020-090
Route of Administration	ORAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
brigatinib (UNII: HYW8DB273J) (brigatinib - UNII:HYW8DB273J)	brigatinib	90 mg

Inactive Ingredients	
Ingredient Name	**Strength**
Lactose monohydrate (UNII: EWQ57Q8I5X)	
Microcrystalline cellulose (UNII: OP1R32D61U)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
Magnesium stearate (UNII: 70097M6I30)	

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	OVAL	**Size**	15mm
Flavor		**Imprint Code**	U7
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63020-090-07	7 in 1 BOTTLE; Type 1: Convenience Kit of Co-Package		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208772	04/28/2017	

Part 2 of 2

ALUNBRIG

brigatinib tablet, film coated

Product Information

Item Code (Source)	NDC:63020-180
Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
brigatinib (UNII: HYW8DB273J) (brigatinib - UNII:HYW8DB273J)	brigatinib	180 mg

Inactive Ingredients

Ingredient Name	Strength
Lactose monohydrate (UNII: EWQ57Q8I5X)	
Microcrystalline cellulose (UNII: OP1R32D61U)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
Magnesium stearate (UNII: 70097M6I30)	

Product Characteristics

Color	WHITE	**Score**	no score
Shape	OVAL	**Size**	19mm
Flavor		**Imprint Code**	U13
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63020-180-23	23 in 1 BOTTLE; Type 1: Convenience Kit of Co-Package		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208772	04/28/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208772	04/28/2017	

Labeler - Takeda Pharmaceuticals America, Inc. (039997266)

Establishment

Name	Address	ID/FEI	Business Operations
AMPAC Fine Chemicals LLC		073903937	API MANUFACTURE(63020-113, 63020-090, 63020-180, 63020-198) , ANALYSIS(63020-113, 63020-090, 63020-180, 63020-198)

Establishment

Name	Address	ID/FEI	Business Operations
Curia New York, Inc.		124193793	ANALYSIS(63020-113, 63020-090, 63020-180, 63020-198) , API MANUFACTURE(63020-113, 63020-090, 63020-180, 63020-198)

Establishment

Name	Address	ID/FEI	Business Operations
Ajinomoto Omnichem		400344443	API MANUFACTURE(63020-113, 63020-090, 63020-180, 63020-198) , ANALYSIS(63020-113, 63020-090, 63020-180, 63020-198)

Establishment

Name	Address	ID/FEI	Business Operations
Solvias AG		480739627	ANALYSIS(63020-113, 63020-090, 63020-180, 63020-198)

Establishment

Name	Address	ID/FEI	Business Operations
Penn Pharmaceutical Services Limited		226277259	MANUFACTURE(63020-113, 63020-090, 63020-180, 63020-198) , ANALYSIS(63020-113, 63020-090, 63020-180, 63020-198) , PACK(63020-113, 63020-090, 63020-180, 63020-198) , LABEL(63020-113, 63020-090, 63020-180, 63020-198)

Establishment

Name	Address	ID/FEI	Business Operations
Almac Sciences (Ireland) Limited		985822621	ANALYSIS(63020-113, 63020-090, 63020-180, 63020-198)

Establishment

Name	Address	ID/FEI	Business Operations
Takeda Ireland Limited		988980314	MANUFACTURE(63020-113, 63020-090, 63020-180, 63020-198) , ANALYSIS(63020-113, 63020-090, 63020-180, 63020-198) , PACK(63020-113, 63020-090, 63020-180, 63020-198) , LABEL(63020-113, 63020-090, 63020-180, 63020-198)

Revised: 1/2026 Takeda Pharmaceuticals America, Inc.