Brigatinib (Systemic)

Alunbrig® (https://www.alunbrig.com)

Antineoplastic agent; an inhibitor of multiple tyrosine kinases, including anaplastic lymphoma kinase (ALK).

USES

Non-small Cell Lung Cancer (NSCLC)

Treatment of ALK-positive metastatic NSCLC (designated an orphan drug by FDA for treatment of ALK-positive, c-ros oncogene-1 [ROS-1]-positive, or epidermal growth factor receptor [EGFR] mutation-positive NSCLC).

Guidelines for the treatment of stage IV NSCLC in patients with ALK driver alterations generally support the use of brigatinib as an option in the first-line setting and in the second-line setting following therapy with crizotinib.

DOSAGE AND ADMINISTRATION

General

Pretreatment Screening

1. Control blood pressure before initiating therapy.
2. Measure fasting serum glucose concentrations prior to initiating therapy, and initiate or optimize antihyperglycemic therapy as clinically indicated.

Patient Monitoring

1. Monitor blood pressure 2 weeks after starting therapy and at least monthly thereafter.
2. Monitor heart rate during therapy. More frequent monitoring may be necessary in patients receiving concomitant therapy with drugs known to cause bradycardia.
3. Monitor serum creatine kinase (CK, creatine phosphokinase, CPK) and pancreatic enzyme (e.g., amylase, lipase) concentrations during therapy.
4. Measure fasting serum glucose concentrations periodically during therapy.
5. Monitor for new or worsening respiratory symptoms, particularly during the initial week of therapy.
6. Monitor for visual disturbances.
7. Monitor AST, ALT, and total bilirubin during treatment, especially during the first 3 months.

Other General Considerations

1. Advise patients to limit sun exposure (e.g., wear protective clothing and sunscreen) during therapy and for at least 5 days after discontinuing the drug.

Administration and Preparation

Oral Administration

Administer once daily without regard to food. Swallow tablets whole; do not crush or chew tablets.

Dosage

Adults

NSCLC

Oral

90 mg once daily for first 7 days, then increase to 180 mg once daily. Continue therapy until disease progression or unacceptable toxicity occurs.

Following treatment interruptions lasting ≥14 days for reasons other than adverse reactions, resume brigatinib at a dosage of 90 mg once daily for 7 days, then increase to the previously tolerated dosage.

Dosage Modification for Toxicity

In the ALTA study, 7.3 or 20% of patients receiving 90 mg once daily or 180 mg once daily, respectively, required dosage reduction (most commonly for elevated serum CK concentrations). In the ALTA 1L trial, dosage reduction because of any adverse event occurred in 29% of patients treated with brigatinib 180 mg once daily.

If dosage reduction is necessary in patients receiving 90 mg once daily, initially reduce dosage to 60 mg once daily. If further dosage reduction is needed, permanently discontinue the drug.

If dosage reduction is necessary in patients receiving 180 mg once daily, initially reduce dosage to 120 mg once daily. If further dosage reduction is needed, reduce dosage to 90 mg once daily. If dosage reduction from 90 mg once daily is necessary, reduce dosage to 60 mg once daily. If further dosage reduction is needed, permanently discontinue the drug.

Once dosage has been reduced because of adverse reactions, do not subsequently increase dosage.

Interstitial Lung Disease/Pneumonitis

If new grade 1 pulmonary symptoms occur during the first 7 days of treatment, interrupt therapy until recovery to baseline. May resume brigatinib at the same dosage; do not increase dosage to 180 mg once daily if interstitial lung disease (ILD)/pneumonitis is suspected.

If new grade 1 pulmonary symptoms occur after the first 7 days of treatment, interrupt therapy until recovery to baseline; may resume brigatinib at same dosage.

If new grade 2 pulmonary symptoms occur during the first 7 days of treatment, interrupt therapy until recovery to baseline. May resume brigatinib at the next lower dosage; do not increase dosage if ILD/pneumonitis is suspected.

If new grade 2 pulmonary symptoms occur after the first 7 days of treatment, interrupt therapy until recovery to baseline. If ILD/pneumonitis is suspected, may resume brigatinib at the next lower dosage; otherwise, may resume therapy at the same dosage.

If grade 1 or 2 ILD/pneumonitis recurs, permanently discontinue brigatinib.

If grade 3 or 4 ILD/pneumonitis occurs, permanently discontinue brigatinib.

Hypertension

If grade 3 hypertension (i.e., SBP ≥160 mm Hg or DBP ≥100 mm Hg, requiring medical intervention and >1 antihypertensive agent or more intensive therapy than previously used) occurs, interrupt therapy until recovery to grade 1 or less hypertension (i.e., SBP <140 mm Hg and DBP <90 mm Hg); may then resume brigatinib at the next lower dosage.

If grade 3 hypertension recurs, interrupt therapy until recovery to grade 1 or less hypertension; may then resume brigatinib at the next lower dosage or permanently discontinue the drug.

If grade 4 hypertension (i.e., life-threatening consequences, requiring urgent intervention) occurs, interrupt therapy until recovery to grade 1 or less hypertension; may then resume brigatinib at the next lower dosage or permanently discontinue the drug.

If grade 4 hypertension recurs, permanently discontinue brigatinib.

Bradycardia

If symptomatic, but non-life-threatening, bradycardia occurs, interrupt brigatinib therapy until recovery to asymptomatic bradycardia or to a resting heart rate of ≥60 beats/minute. If concomitant therapy includes drugs known to cause bradycardia and is modified (dosage adjusted or drug discontinued), may resume brigatinib at same dosage; if such modification is not possible or if no concomitant contributory drugs are identified, may resume brigatinib at next lower dosage.

If life-threatening bradycardia requiring urgent intervention occurs in patients receiving concomitant contributory drugs known to cause bradycardia, interrupt brigatinib therapy until recovery to asymptomatic bradycardia or to a resting heart rate of ≥60 beats/minute. If the concomitant therapy is

modified, may resume brigatinib at the next lower dosage with frequent monitoring as clinically indicated; permanently discontinue brigatinib in case of recurrence.

If life-threatening bradycardia requiring urgent intervention occurs in patients not receiving concomitant contributory drugs, permanently discontinue brigatinib.

Visual Disturbances

If grade 2 or 3 visual disturbance occurs, interrupt therapy until recovery to grade 1 or baseline; may resume therapy at next lower dosage.

If grade 4 visual disturbance occurs, permanently discontinue brigatinib.

CK Elevation

If serum CK concentrations >5 times ULN (i.e., grade 3), interrupt therapy until CK concentrations return to baseline or ≤2.5 times ULN (i.e., grade 1 or less); may resume brigatinib at same dosage. If serum CK concentrations >5 times ULN r ecur, interrupt therapy until CK concentrations return to baseline or ≤2.5 times ULN; may resume brigatinib at the next lower dosage.

If serum CK concentrations >10 times ULN (i.e., grade 4), interrupt therapy until serum CK concentrations return to baseline or ≤2.5 times ULN; may resume brigatinib at the next lower dosage.

Pancreatic Enzyme Elevation

If serum amylase or lipase concentrations >2 times the ULN (i.e., grade 3), interrupt therapy until amylase or lipase concentrations recover to baseline or ≤1.5 times ULN (i.e., grade 1 or less); may resume brigatinib at same dosage. If grade 3 amylase or lipase elevation recurs, interrupt therapy until amylase or lipase concentrations recover to baseline or ≤1.5 times ULN (i.e., grade 1 or less); may resume brigatinib at the next lower dosage.

If serum amylase or lipase concentrations >5 times ULN (i.e., grade 4), interrupt therapy until amylase or lipase concentrations recover to baseline values or ≤1.5 times ULN (i.e., grade 1 or less); may resume brigatinib at the next lower dosage.

Hepatotoxicity

If grade 3 or 4 elevation (>5 times the ULN) of either AST or ALT with bilirubin ≤2 times the ULN occurs, withhold therapy until recovery to grade 1 or less (≤3 times the ULN) or to baseline. Resume brigatinib at the next lower dose.

If grade 2 to 4 elevation (>3 times the ULN) of ALT or AST with concurrent total bilirubin elevation >2 times the ULN in the absence of cholestasis or hemolysis occurs, permanently discontinue brigatinib.

Hyperglycemia

If hyperglycemia occurs with serum glucose concentrations >250 mg/dL (i.e., grade 3) and adequate hyperglycemic control cannot be achieved despite optimal antidiabetic agent therapy, interrupt brigatinib therapy until adequate control of hyperglycemia is achieved. Consider resuming brigatinib at the next lower dosage or permanent discontinuance of the drug.

Other Toxicity

If other grade 3 adverse reaction occurs, interrupt therapy until recovery to baseline; may resume brigatinib at same dosage. If the grade 3 adverse reaction recurs, interrupt therapy until recovery to baseline; may resume brigatinib at the next lower dosage or discontinue drug.

If other grade 4 adverse reaction occurs, interrupt therapy until recovery to baseline; may resume brigatinib at the next lower dosage or permanently discontinue drug. If the grade 4 adverse reaction recurs, permanently discontinue brigatinib.

Concomitant Use of Drugs Affecting Hepatic Microsomal Enzymes

Inhibitors of CYP3A

Avoid concomitant use of brigatinib with drugs that are potent or moderate inhibitors of CYP3A.

If concomitant use of a potent CYP3A inhibitor cannot be avoided, reduce once daily dosage of brigatinib by approximately 50% (e.g., from 180 mg to 90 mg once daily; from 90 mg to 60 mg once daily).

If concomitant use of a moderate CYP3A inhibitor cannot be avoided, reduce dosage of brigatinib by approximately 40% (e.g., from 180 mg to 120 mg once daily; from 120 mg to 90 mg once daily; from 90 mg to 60 mg once daily).

If concomitant use of the potent or moderate CYP3A inhibitor is discontinued, resume brigatinib dosage that was tolerated prior to initiation of the CYP3A inhibitor.

Inducers of CYP3A

Avoid concomitant use of brigatinib with drugs that are potent or moderate inducers of CYP3A.

If concomitant use of a moderate CYP3A inducer cannot be avoided, increase dosage of brigatinib in 30-mg increments (as tolerated) after 7 days of therapy, up to a maximum of twice the brigatinib dose that was tolerated prior to initiation of the moderate CYP3A inducer.

If concomitant use of the moderate CYP3A inducer is discontinued, resume the brigatinib dose that was tolerated prior to initiation of the moderate CYP3A inducer.

Special Populations

Mild or moderate hepatic impairment (Child-Pugh class A or B): No dosage adjustment needed.

Severe hepatic impairment (Child-Pugh class C): Reduce dosage by approximately 40% (e.g., from 180 mg to 120 mg once daily; from 120 mg to 90 mg once daily; from 90 mg to 60 mg once daily).

Mild or moderate renal impairment (Cl_{cr} 30–89 mL/minute): No dosage adjustment needed.

Severe renal impairment (Cl_{cr} 15–29 mL/minute): Reduce dosage by approximately 50% (e.g., from 180 mg to 90 mg once daily; from 90 mg to 60 mg once daily).

Geriatric Patients

No specific dosage recommendations.

Cautions

Contraindications

1. Manufacturer states none known.

Warnings and Precautions

Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, or fatal adverse pulmonary reactions consistent with ILD/ pneumonitis may occur. Adverse pulmonary symptoms consistent with possible ILD/pneumonitis occur early (i.e., within 8–9 days of initiation of therapy).

Monitor patients for new or worsening respiratory symptoms, particularly during first week of therapy. If respiratory symptoms occur, interrupt therapy and promptly evaluate for ILD/pneumonitis or other potential causes (e.g., pulmonary embolism, tumor progression, pneumonia). If ILD/pneumonitis is confirmed or ILD/pneumonitis recurs, dosage reduction or discontinuance of therapy may be necessary depending on the severity.

Hypertension

Hypertension reported.

Control BP before initiating brigatinib therapy and monitor BP 2 weeks after treatment initiation and at least monthly during treatment.

If severe hypertension occurs despite optimal antihypertensive therapy, interrupt therapy until BP is controlled; dosage reduction or discontinuance of therapy may be necessary. Consider permanent discontinuance of brigatinib if grade 4 hypertension occurs or if grade 3 hypertension recurs.

Bradycardia

Bradycardia reported.

Monitor heart rate and BP periodically during brigatinib therapy; monitor more frequently if concurrent use of a drug known to cause bradycardia cannot be avoided.

If symptomatic or life-threatening bradycardia occurs, interrupt therapy; dosage reduction or discontinuance of brigatinib therapy may be necessary depending on concomitant use of other drugs known to cause bradycardia. Evaluate concomitant therapy to identify any drugs that may cause bradycardia; adjust dosage or discontinue such drugs, if possible. If concomitant therapy with a drug known to cause bradycardia is identified and subsequently discontinued or the dosage is adjusted, resume brigatinib at the same dosage following resolution of symptomatic bradycardia. If no concomitant therapy with a drug known to cause bradycardia is identified, reduce the dosage of brigatinib following resolution of symptomatic bradycardia. Discontinue brigatinib if life-threatening bradycardia occurs in the absence of contributing concomitant medications.

Visual Disturbances

Visual disturbances, including blurred vision, diplopia, and reduced visual acuity, reported; macular edema and cataract also reported.

If new or worsening visual disturbances of grade 2 or greater severity occur, interrupt therapy and obtain ophthalmologic evaluation. Dosage reduction or drug discontinuance may be required depending on the severity of ocular effects.

CK Elevation

Serum CK elevations reported.

Monitor serum CK concentrations periodically. If CK elevation occurs, temporary interruption followed by resumption of therapy at same dosage or at a reduced dosage may be necessary depending on the severity.

Pancreatic Enzyme Elevation

Serum amylase and/or lipase elevations reported.

Monitor serum amylase and lipase concentrations periodically during therapy. If amylase and/or lipase elevation occurs, temporary interruption followed by resumption of therapy at same dosage or at a reduced dosage may be necessary depending on the severity.

Hepatotoxicity

Hepatotoxicity reported.

Monitor AST, ALT, and total bilirubin during treatment, especially during the initial 3 months. Withhold therapy for grade 3 or 4 hepatic enzyme elevation with bilirubin ≤2 times the ULN. Resume brigatinib at a next lower dose upon resolution or recovery to grade 1 or less (≤3 times the ULN) or to baseline. Permanently discontinue therapy for grade 2 to 4 hepatic enzyme elevation with concurrent total bilirubin elevations >2 times the ULN in the absence of cholestasis or hemolysis.

Hyperglycemia

Hyperglycemia reported.

Measure fasting serum glucose concentrations prior to initiating therapy and periodically monitor during therapy. Initiate or optimize antidiabetic therapy as clinically indicated. If adequate glycemic control cannot be achieved despite optimal medical management, interrupt therapy until hyperglycemia is adequately controlled. Dosage reduction or discontinuance of therapy may be necessary depending on severity of hyperglycemia.

Photosensitivity

Photosensitivity reported.

Advise patients to limit sun exposure during brigatinib therapy, and for at least 5 days after discontinuation of treatment. Counsel patients to wear a hat and protective clothing when outdoors, and to use a broad-spectrum sunscreen and lip balm (SPF ≥30) for protection against sunburn.

Fetal/Neonatal Morbidity and Mortality

May cause fetal harm; dose-related skeletal abnormalities, increased post-implantation loss, malformations, and decreased fetal body weight observed in animals.

Avoid pregnancy during therapy. Females of reproductive potential should use effective nonhormonal methods of contraception during therapy and for ≥4 months after drug discontinuance. If used during pregnancy or if patient becomes pregnant, apprise of potential fetal hazard.

Males with female partners of reproductive potential should use effective methods of contraception during therapy and for ≥3 months after drug discontinuance.

Specific Populations

Pregnancy

May cause fetal harm.

Lactation Not known whether brigatinib is distributed into milk or if drug has any effect on milk production or the breast-fed infant. Females should not breast-feed during therapy and for ≥1 week after drug discontinuance.

Females and Males of Reproductive Potential Verify pregnancy status in females of reproductive potential prior to initiating brigatinib therapy. Advise females of reproductive potential to use effective contraception during therapy and for at least 4 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during brigatinib therapy and for at least 3 months after the final dose.

Based on findings from animal studies, brigatinib may reduce fertility in males.

Pediatric Use Safety and efficacy not established in pediatric patients.

Geriatric Use Insufficient experience in patients ≥65 years of age to determine whether they respond differently than younger adults. In the principal efficacy studies, no clinically important differences in safety or efficacy observed between geriatric patients and younger adults.

Hepatic Impairment Mild hepatic impairment (total bilirubin not exceeding ULN with AST exceeding ULN, or total bilirubin >1 to 1.5 times ULN with any AST): Exposure not altered; no dosage adjustment necessary. Severe hepatic impairment (Child-Pugh class C): Following a single 90-mg dose of brigatinib, the AUC of brigatinib was 37% higher compared to individuals with normal hepatic function. Reduce dosage of brigatinib.

Renal Impairment Exposure not altered by mild or moderate renal impairment (Cl_{cr} 30–89 mL/minute). No dosage adjustment necessary.

Pharmacokinetics and safety not studied in patients with severe renal impairment (Cl_{cr} <30 mL/ minute). Following a single 90-mg dose of brigatinib, AUC of brigatinib was 86% higher in patients with severe renal impairment (Cl_{cr} 15–29 mL/minute) compared to individuals with normal renal function. Reduce dosage of brigatinib.

Common Adverse Effects

The most common adverse reactions (reported in ≥25% of patients): Diarrhea, fatigue, nausea, rash, cough, myalgia, headache, hypertension, vomiting, dyspnea.

Drug Interactions

Metabolized principally by CYP isoenzymes 2C8 and 3A4.

Substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in vitro; not a substrate of organic anion transport protein (OATP) 1B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 1, OCT2, multidrug and toxin extrusion transporter (MATE) 1, MATE2K, or bile salt export pump (BSEP).

In vitro, inhibits P-gp, BCRP, OCT1, MATE1, and MATE2K; does not inhibit OATP1B1, OATP1B3, OAT1, OAT3, OCT2, or BSEP.

Induces CYP3A and also may induce CYP2C isoenzymes via activation of the pregnane X receptor (PXR). Brigatinib and its principal metabolite do not inhibit CYP isoenzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5.

Drugs and Foods Affecting Hepatic Microsomal Enzymes

Potent or moderate CYP3A inhibitors: Possible pharmacokinetic interaction (increased plasma concentrations of brigatinib and risk of adverse effects). Avoid concomitant use. If concomitant use of a potent CYP3A inhibitor cannot be avoided, reduce daily dosage of brigatinib by approximately 50% (e.g., from 180 mg daily to 90 mg daily or from 90 mg daily to 60 mg daily). If concomitant use of a moderate CYP3A inhibitor cannot be avoided, reduce the once daily dose of brigatinib by approximately 40% (e.g., from 180 mg to 120 mg once daily; from 120 mg to 90 mg once daily; from 90 mg to 60 mg once daily). If the potent or moderate CYP3A inhibitor is discontinued, resume brigatinib therapy at the dosage that was tolerated prior to initiation of the potent CYP3A inhibitor.

CYP2C8 inhibitors: Clinically important pharmacokinetic interactions unlikely.

Potent or moderate CYP3A inducers: Possible pharmacokinetic interaction (decreased plasma concentrations of brigatinib and possible reduced efficacy). Avoid concomitant use. If concomitant use of a moderate CYP3A inducer cannot be avoided, increase the dosage of brigatinib in 30-mg increments (as tolerated) after 7 days of therapy, up to a maximum of twice the brigatinib dose that was tolerated prior to initiation of the moderate

CYP3A inducer. If concomitant use of the moderate CYP3A inducer is discontinued, resume the brigatinib dose that was tolerated prior to initiation of the moderate CYP3A inducer.

Inhibitors of P-gp or BCRP

Inhibitors of P-gp or BCRP: Clinically important pharmacokinetic interactions unlikely.

Drugs Metabolized by Hepatic Microsomal Enzymes

Substrates of CYP3A: Possible pharmacokinetic interaction (decreased plasma concentrations and possible reduced efficacy of CYP3A substrate).

Substrates of Drug Transport Systems

Substrates of P-gp, BCRP, OCT1, MATE1, or MATE2K: Possible pharmacokinetic interaction (increased plasma concentrations of P-gp, BCRP, OCT1, MATE1, or MATE2K substrate).

Drugs Associated with Bradycardia

Possible increased risk of bradycardia; use with caution. If concomitant use cannot be avoided, monitor heart rate more frequently. If clinically important bradycardia occurs, discontinue or adjust dosage of the concomitant drug, if possible.

Specific Drugs and Foods

Drug or Food	Interaction	Comments
Antifungals, azoles (e.g., itraconazole)	Potent or moderate CYP3A inhibitors: Possible increased brigatinib concentrations and adverse effects Brigatinib AUC and peak concentrations increased by 101 and 21%, respectively	Potent CYP3A inhibitors: Avoid concomitant use; if concomitant use cannot be avoided, reduce dosage of brigatinib by approximately 50% (e.g., from 180 to 90 mg daily or from 90 to 60 mg daily) Moderate CYP3A inhibitors: Avoid concomitant use; if concomitant use cannot be avoided, reduce dosage of brigatinib by approximately 40% (e.g., from 180 mg to 120 mg once daily; from 120 mg to 90 mg once daily; from 90 mg to 60 mg once daily) If the antifungal is discontinued, resume brigatinib at the dosage that was tolerated prior to initiation of the antifungal
Gemfibrozil	Decreased brigatinib AUC and peak concentrations, not considered clinically important	
Grapefruit or grapefruit juice	Possible increased brigatinib concentrations	Avoid concomitant use
Rifampin	Brigatinib AUC and peak concentrations decreased by 80 and 60%, respectively	Avoid concomitant use

Pharmacokinetics

Bioavailability

Peak plasma concentrations of brigatinib attained 1–4 hours following oral administration.

Systemic exposure to brigatinib is dose proportional over an oral dosage range of 60–240 mg following single or repeat dosing.

Food

High-fat meal decreased peak plasma concentrations of brigatinib by 13% but had no effect on systemic exposure compared with administration in the fasting state.

Special Populations

Mild or moderate hepatic impairment does not affect exposure to brigatinib. Exposure increased in severe hepatic impairment.

Mild or moderate renal impairment does not affect exposure to brigatinib. Exposure increased in severe renal impairment.

Age, sex, race, body weight, and serum albumin concentration do not substantially affect brigatinib pharmacokinetics.

Extent

Not known whether distributed into human milk.

Plasma Protein Binding

66%; independent of drug concentration.

Metabolism

Principally metabolized by CYP2C8 and CYP3A4.

Major active metabolite (AP26123) inhibits ALK with approximately threefold lower potency than brigatinib.

Systemic exposure of AP26123 is <10% of parent drug.

Elimination Route

Eliminated in feces (65%; 41% as unchanged drug) and urine (25%; 86% as unchanged drug).

Half-life

25 hours.

Stability

Storage

Oral

Tablets

20–25°C (excursions permitted between 15–30°C).

Actions

1. Inhibits multiple tyrosine kinases, including ALK, c-ros oncogene-1 (ROS-1), insulin-like growth factor receptor-1 (IGFR-1), and fms-like tyrosine kinase 3 (FLT-3) as well as epidermal growth factor receptor (EGFR) deletion and point mutations.
2. Inhibits ALK phosphorylation and ALK-mediated activation of the downstream signaling proteins signal transducer and activator of transcription 3 (STAT3), AKT serine/ threonine kinase, extracellular signal-regulated kinase (ERK) 1/2, and ribosomal protein S6 in vitro and in vivo.
3. Activating mutations or translocations of the ALK gene identified in several malignancies and can result in the expression of oncogenic fusion proteins (e.g., echinoderm microtubule-associated protein-like 4 [EML4]-ALK). Formation of ALK fusion proteins results in activation and dysregulation of the gene's expression and signaling, which can contribute to increased cell proliferation and survival in tumors expressing these proteins.

4. ALK rearrangements identified in approximately 3–7% of patients with NSCLC.
5. Clinical resistance to crizotinib attributed to several possible mechanisms, including acquired resistance mutations of ALK, amplification of gene expression, and activation of alternate signaling pathways. CNS is a common site of disease progression in crizotinib-treated patients because of poor distribution of the drug into CSF.
6. Brigatinib is approximately 12-fold more potent than crizotinib against native ALK-positive cell lines in vitro.
7. Brigatinib is active against cells expressing EML4-ALK and nucleophosmin (NPM)-ALK fusion proteins and many mutant forms associated with resistance to alectinib, ceritinib, and/or crizotinib, as well as EGFR-Del (E746-A750), ROS1-L2026M, FLT3F691L, and FLT3-D835Y.
8. Exhibits dose-dependent antitumor activity in mice bearing NSCLC tumor xenografts expressing EML4-ALK, including several with ALK mutations conferring resistance to crizotinib, ceritinib, and alectinib (e.g., L1196M, G1202R).
9. Demonstrates reduced tumor burden and prolonged survival in mice bearing intracranial ALK-positive NSCLC tumor xenografts. Demonstrated antitumor activity in patients with crizotinib-resistant ALK-positive NSCLC with baseline CNS metastases.

Advice to Patients

1. Instruct patients to read the manufacturer's patient information.
2. Advise patients to take brigatinib exactly as prescribed and to not alter the dosage or discontinue therapy unless advised to do so by their clinician. Advise patients to swallow brigatinib tablets whole without regard to food and not to crush or chew the tablets. If a dose is missed or if vomiting occurs after a dose is administered, the next dose should be taken at the regularly scheduled time; the missed dose should not be taken, and an additional dose should not be administered to replace the vomited dose.
3. Inform patients of the symptoms and risks of serious adverse pulmonary reactions such as ILD/pneumonitis, which occur particularly during the first week of brigatinib therapy. Advise patients to immediately report any new or worsening pulmonary symptoms (e.g., dyspnea or shortness of breath, cough with or without mucus, chest pain, fever) to their clinician and inform them that such symptoms may be similar to those of lung cancer.
4. Risk of hypertension. Advise patients to promptly report signs or symptoms of hypertension (e.g., headache, dizziness, blurred vision, chest pain, shortness of breath).
5. Risk of bradycardia. Advise patients to immediately contact their clinician if they experience dizziness, lightheadedness, or faintness.
6. Risk of visual disturbances. Advise patients to inform clinician of any new or worsening visual symptoms (e.g., diplopia, blurred vision, flashes of light, photophobia, new or increased floaters).
7. Risk of muscle problems or myalgia; importance of CK monitoring. Inform patients to promptly report any new or worsening signs or symptoms of muscle problems (e.g., unexplained or persistent muscle pain, tenderness, weakness).
8. Risk of elevated concentrations of pancreatic enzymes and importance of monitoring amylase and lipase concentrations. Inform patients to immediately contact their clinician if they experience manifestations of pancreatitis (e.g., upper abdominal pain that may spread to the back and get worse with eating, weight loss, nausea).
9. Risk of new or worsening hyperglycemia and importance of periodically monitoring blood glucose concentrations. Immediately inform clinician if manifestations of hyperglycemia occur (e.g., increased thirst, increased urination, increased appetite, nausea, weakness, fatigue, confusion). Patients with diabetes mellitus or glucose intolerance may require dosage adjustment of antidiabetic therapy during brigatinib treatment.
10. Risk of hepatotoxicity. Inform patients of the signs and symptoms of hepatotoxicity (e.g., yellowing of the skin or whites of the eyes, dark urine, nausea or vomiting, feeling tired, decreased appetite) and the need to monitor for liver function during treatment. Advise patients to inform their clinician of any new or worsening symptoms.
11. Risk of photosensitivity. Advise patients to limit sun exposure while taking brigatinib and for at least 5 days after discontinuance of the drug.

12. Risk of fetal harm. Advise females of reproductive potential that they should use effective, nonhormonal methods of contraception while receiving brigatinib and for ≥4 months after discontinuance of therapy and advise such females that oral contraceptives and other hormonal forms of contraception may not be effective during brigatinib therapy. Advise males with female partners of reproductive potential to use effective methods of contraception while receiving the drug and for ≥3 months after the drug is discontinued. Also advise males that brigatinib may cause fertility problems and to discuss any concerns about fertility with their clinician.
13. Importance of females informing their clinicians if they are or plan to become pregnant. If pregnancy occurs, advise of potential fetal risk.
14. Advise females to avoid breast-feeding while receiving brigatinib and for ≥1 week after discontinuance of therapy.
15. Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs (e.g., cardiac or antihypertensive agents, antidiabetic agents) and dietary or herbal supplements (e.g., St. John's wort, grapefruit-containing products), as well as any concomitant illnesses (e.g., cardiovascular disease, diabetes mellitus, pancreatitis).
16. Advise patients to avoid grapefruit and grapefruit juice while taking brigatinib.
17. Inform patients of other important precautionary information.

Preparations

Restricted Distribution

Brigatinib can only be obtained through a limited network of specialty pharmacies. Consult manufacturer's website for specific information regarding distribution of the drug.

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Brigatinib [Generic Name]

Route Section

Tablets, film-coated

[NDC: ; RXCUI:] **Alunbrig® ,**
30 mg Ariad

[NDC: ; RXCUI:] **Alunbrig® ,**
90 mg Ariad

[NDC: ; RXCUI:] **Alunbrig® ,**
180 mg Ariad