

DRUG NAME: Brigatinib

SYNONYM(S): AP26113¹

COMMON TRADE NAME(S): ALUNBRIG®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Brigatinib is an orally administered broad spectrum tyrosine kinase inhibitor. It targets anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS-1), insulin-like growth factor receptor-1 (IGF-R1), fms-like tyrosine kinase 3 (FLT-3), and epidermal growth factor receptor (EGFR) deletion and point mutations. Brigatinib inhibits ALK autophosphorylation and ALK-mediated phosphorylation of downstream signaling proteins STAT3, AKT, ERK1/2, and S6. *In vitro*, brigatinib also inhibits the proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins, and the viability of cells expressing EML4-ALK and 17 mutant forms associated with resistance to other ALK inhibitors. Brigatinib has *in vivo* clinical activity against multiple mutant forms of EML4-ALK, including G1202R and L1196M.¹⁻⁴

PHARMACOKINETICS:

Oral Absorption	dose proportional systemic exposure; T _{max} = 1-4 hours	
Distribution	blood to plasma ratio = 0.69	
	cross blood brain barrier?	no information found
	volume of distribution	307 L
	plasma protein binding	91% (not concentration-dependent)
Metabolism	primarily metabolized by CYP 3A4 and CYP 2C8	
	active metabolite(s)	AP26123 (3-fold lower potency than brigatinib <i>in vitro</i>)
	inactive metabolite(s)	no information found
Excretion	primarily fecal elimination	
	urine	25% (86% as unchanged drug)
	feces	65% (41% as unchanged drug)
	terminal half life	25 h
	clearance	8.9 L/h
Sex	no clinically meaningful effect	
Elderly	no clinically meaningful effect	
Ethnicity	no clinically meaningful effect	

Adapted from standard reference³ unless specified otherwise.

USES:

Primary uses:

*Lung cancer, non-small cell³

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:

- **bradycardia** and prolongation of the PR interval have been reported; caution is required in patients with low heart rate at baseline, or those who have a history of syncope, arrhythmia, conduction disorders, ischemic heart disease, congestive heart failure, or are taking other medications which decrease heart rate or prolong the PR interval³
- **hyperglycemia** is reported; assess fasting serum glucose prior to starting treatment, particularly in patients with diabetes³
- **visual disturbances** have been reported; ability to drive or operate machinery may be compromised³

Special populations: patients **aged 65 years and older** have an increased risk of experiencing early pulmonary adverse reactions³

Carcinogenicity: no information found

Mutagenicity: not mutagenic in Ames test and mammalian *in vitro* mutation test. Brigatinib is aneugenic in mammalian *in vivo* chromosome test at exposures much higher than those seen following human clinical exposure. Genotoxic risk is not expected in humans.³

Fertility: in animal studies, testicular toxicity occurred at exposures lower than those seen following human clinical exposure. Non-reversible findings in the male reproductive system included testicular tubular degeneration and reduced weight of the testes, seminal vesicles, and prostate gland. Reduced testes size and microscopic evidence of hypospermatogenesis were reversible findings. No effects on female reproductive organs were observed in animal studies.³

Pregnancy: in animal studies, dose-related skeletal anomalies, including embryo-lethality, reduced fetal growth, and skeletal variations, were observed at lower exposures than those seen following human clinical exposure. Increased post-implantation loss, malformations (e.g., anasarca, anophthalmia, bent limbs, fused ribs, omphalocele and gastroschisis), and decreased fetal body weight were observed at exposures approximately equal to those seen following human clinical exposure. Women of childbearing potential should use effective contraception during treatment and for at least 4 months following the last dose. Men with female partners of childbearing potential should use effective contraception during treatment and for at least 3 months following the last dose. Brigatinib may reduce the effectiveness of hormonal contraceptives via CYP 3A4 induction; alternative contraceptive measures are recommended.^{3,4}

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should wait at least 1 week following the last dose before breastfeeding.³

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important⁵.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
blood and lymphatic system/ febrile neutropenia	anemia (36-49%, severe <2%)
	lymphopenia (20-42%, severe 4-13%)
	neutropenia (12-24%, severe 4%)
	thrombocytopenia (10%)
cardiac	bradycardia (5-12%, severe <1%); see paragraph following Side Effects table
	palpitations (5%)
eye	visual disturbance (7-16%, severe <2%); see paragraph following Side Effects table
gastrointestinal	<i>emetogenic potential: moderate</i> ⁶
	abdominal pain (10-24%, severe <2%)
	constipation (15-20%)
	diarrhea (38-53%, severe 2%)
	dry mouth (5-9%)
	dyspepsia (6-8%, severe <1%)
	gastroesophageal reflux disease (<1%)
	nausea (30-47%, severe 1-2%)
	stomatitis (8-13%, severe <1%)
	vomiting (21-30%, severe <1%)
general disorders and administration site conditions	edema (11-18%, severe <1%)
	fatigue (32-42%, severe <2%)
	malaise (4%)
	multiple organ dysfunction syndrome (<1%); fatal events reported
	non-cardiac chest pain (4%, severe <1%)
	pyrexia (3-15%, severe <1%)
infections and infestations	nasopharyngitis (8%)
	pneumonia (4-15%, severe 5-6%); fatal events reported
	upper respiratory tract infection (12%)
	urinary tract infection (6%, severe <1%)
investigations	albumin decrease (15-50%, severe 4%)
	amylase increase (24-52%, severe 3-7%); median time to onset = 16-29 days
	alkaline phosphatase increase (29-47%, severe <3%)
	ALT increase (40-75%, severe 3-12%)
	AST increase (65-72%, severe 3-5%)
	blood cholesterol increase (13%)
	blood lactate dehydrogenase increase (4%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	calcium decrease (15-64%, severe 2%)
	creatinine phosphokinase increase (48-81%, severe 4-24%); see paragraph following Side Effects table
	creatinine increase (15-33%)
	gamma-glutamyl transferase increase (2%, severe 2%)
	lipase increase (35-59%, severe 5-17%); median time to onset = 16-29 days
	magnesium decrease (7-21%)
	phosphorous decrease (23-41%, severe 4-6%)
	potassium increase (22-31%, severe 2-4%)
	PR prolongation
	prolonged activated partial thromboplastin time (20-28%, severe <1%)
	QTc prolongation (5-6%, severe <2%)
	sodium decrease (20%, severe 4%)
	weight increase (2%)
metabolism and nutrition	appetite decrease (9-24%, severe <1%)
	dyslipidemia (3%)
	hyperglycemia (37-67%, severe 4-8%); see paragraph following Side Effects table
musculoskeletal and connective tissue	arthralgia (14-16%)
	back pain (15-21%, severe <2%)
	muscle spasms (17-22%)
	musculoskeletal chest pain (8%)
	musculoskeletal stiffness (1%)
	myalgia (15-28%, severe <1%)
	pain in extremity (4-8%, severe <2%)
nervous system	cerebrovascular accident (<1%); fatal events reported
	dizziness (15%, severe <1%)
	dysgeusia (2-6%)
	headache (22-35%, severe <2%)
	peripheral neuropathy (11-18%, severe <3%)
psychiatric	depression (3%)
	insomnia (7-9%)
respiratory, thoracic and mediastinal	cough (34-40%)
	dysphonia (6%)
	dyspnea (21-26%, severe 2-3%)
	productive cough (9%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i>	
	hypoxia (3%, severe 3%)
	<i>interstitial lung disease (ILD)/pneumonitis</i> (5-10%, severe 3-4%); see paragraph following Side Effects table
skin and subcutaneous tissue	acne (3%)
	dry skin (2-5%)
	<i>photosensitivity reaction</i> (2-4%, severe <1%); see paragraph following Side Effects table
	pruritus (10-20%, severe <1%)
	<i>rash</i> (24-40%, severe 3-5%)
vascular	<i>hypertension</i> (21-32%, severe 6-13%); see paragraph following Side Effects table
	<i>pulmonary embolism</i> (severe 2%); fatal events reported

Adapted from standard reference^{3,4,7} unless specified otherwise.

Bradycardia, sinus bradycardia, and prolongation of the PR interval may occur with brigatinib. Heart rate less than 50 bpm has been reported in up to 8% of patients. Avoid concurrent therapy with medications that also decrease heart rate or prolong the PR interval. For symptomatic bradycardia, withhold brigatinib until patient is asymptomatic or heart rate increases to at least 60 bpm. Dose reduction may be required when treatment resumes. Permanently discontinue brigatinib for life-threatening bradycardia, unless associated with concurrent medications known to cause bradycardia or hypotension. In these patients, withhold brigatinib until patient is asymptomatic or heart rate increases to at least 60 bpm and adjust concurrent therapy as necessary.^{3,4}

Creatine phosphokinase (CPK) elevation is reported in up to 75% of patients, with up to 22% having grade 3 or 4 elevations. Median time to onset is 27 days. Advise patients to report any unexplained muscle pain, tenderness, or weakness. For grade 3 or 4 CPK elevations that occur with grade 2 or higher muscle pain/weakness, withhold brigatinib until symptoms have recovered to at least grade 1 or baseline. Dose reduction may be required when treatment resumes.^{3,4}

New or worsening **hyperglycemia** is reported in 55% of patients and grade 3 elevations in serum glucose have been reported in up to 8%. Initiate or optimize antihyperglycemic medications as needed. Dose interruption, dose reduction, or discontinuation of brigatinib may be required if adequate hyperglycemic control cannot be achieved.^{3,4}

Hypertension, including grade 3 hypertension and hypertensive retinopathy, has been reported. Ensure blood pressure is controlled prior to treatment and monitor blood pressure regularly during treatment. Dose interruption, dose reduction, and/or treatment discontinuation may be required for grade 3 (or higher) hypertension.^{3,4}

Photosensitivity to sunlight has been reported, although severe reactions are not common. To prevent reactions, patients should avoid prolonged sun exposure during treatment with brigatinib and for 5 days after the last dose. Use of broad spectrum UVA/UVB sunscreen and lip protection with at least SPF 30 are recommended. Dose interruption and/or reduction may be required for severe photosensitivity reactions.^{3,7,8}

Pulmonary adverse reactions have been reported, including severe, life-threatening, and fatal reactions and those with features consistent with ILD/pneumonitis. The etiology of pulmonary reactions is not known. Increased age and recent prior treatment with crizotinib (within 7 days) may be independent risk factors. Most reactions are observed within the first 7 days of treatment initiation and usually within the first 24-48 hours. Reactions have also been reported when treatment was resumed following dose interruption. Therefore, monitoring for new or worsening respiratory symptoms during these periods is important. Pneumonitis can also occur later in treatment (median onset of 150 days). Any evidence of pneumonitis should be promptly investigated. Pulmonary reactions are managed with

dose interruption and/or dose reduction. Permanently discontinue brigatinib for grade 3 or 4 reactions, or for recurrence of grade 1 or 2 reactions.^{3,4}

Visual disturbances such as blurred vision, photophobia, photopsia, diplopia, and reduced visual acuity may occur. Severe reactions such as grade 3 macular edema and cataract have been reported. Withhold brigatinib in patients with new or worsening visual symptoms of grade 2 or higher severity. Ophthalmologic evaluation is recommended. Following recovery to grade 1 or baseline, brigatinib may be resumed with dose reduction. Permanently discontinue brigatinib for grade 4 visual disturbances.^{3,4}

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
gemfibrozil ^{3,4}	41% decrease in C _{max} and 12% decrease in AUC of brigatinib	underlying mechanism for decreased exposure unknown	not considered clinically significant; no dose reduction required
grapefruit juice ^{3,4}	may increase plasma level of brigatinib	may inhibit CYP 3A4 metabolism of brigatinib in the intestinal wall	avoid grapefruit juice for 48 hours before and for duration of brigatinib therapy
itraconazole ^{3,4}	21% increase in C _{max} and 101% increase (2-fold) in AUC of brigatinib	strong inhibition of CYP 3A4 by itraconazole	avoid concurrent use; if coadministration cannot be avoided, reduce brigatinib dose from 180 mg to 90 mg (by ~50%) or from 90 mg to 60 mg (by ~30%)
rifampin ^{3,4}	60% decrease in C _{max} and 80% decrease (5-fold) in AUC of brigatinib	strong induction of CYP 3A4 by rifampin	avoid concurrent use

Brigatinib is a substrate of **CYP 3A4**. CYP 3A4 **inhibitors** may increase the plasma concentration of brigatinib. Avoid concurrent use with *moderate* or *strong* CYP 3A4 inhibitors if possible. If coadministration with a *moderate* CYP 3A4 inhibitor cannot be avoided, brigatinib dose reduction is recommended. Reduce brigatinib dose by ~30% (i.e., from 180 mg to 120 mg, 120 mg to 90 mg, or 90 mg to 60 mg). If coadministration with a *strong* CYP 3A4 inhibitor cannot be avoided, reduce brigatinib dose from 180 mg to 90 mg (i.e., by ~50%) or from 90 mg to 60 mg (i.e., by ~30%). After discontinuation of the concurrent inhibitor, brigatinib may be resumed at the prior dose.^{3,4}

CYP 3A4 **inducers** may decrease the plasma concentration of brigatinib. Avoid concurrent use with *moderate* or *strong* CYP 3A4 inducers if possible. If coadministration with a *moderate* CYP 3A4 inducer cannot be avoided, brigatinib dose increase is recommended. After 7 days of concurrent therapy at the current brigatinib dose, increase brigatinib dose in 30 mg increments as tolerated, up to a maximum of twice the prior tolerated brigatinib dose. After discontinuation of the concurrent inducer, brigatinib may be resumed at the prior dose. Concurrent administration with *strong* CYP 3A4 inducers is not recommended; no dosing recommendations are available.^{3,4}

Brigatinib is an **inducer** of **CYP 3A4** *in vitro*. Monitor for loss of efficacy when CYP 3A4 substrates with narrow therapeutic index are coadministered with brigatinib.³

Brigatinib **inhibits** P-gp, BCRP, OCT1, MATE1, and MATE2K *in vitro*. Monitor for increased toxicity when substrates with narrow therapeutic index are coadministered with brigatinib.³

Brigatinib may **induce** pregnane X receptor activation; clinical significance is unknown.³

SUPPLY AND STORAGE:

Oral: Takeda Canada Inc. supplies brigatinib as 30 mg, 90 mg, and 180 mg film-coated tablets. Tablets contain lactose. Store at room temperature.³

Additional information: For starting dose escalation, brigatinib tablets are available as a 28 day initiation pack containing 7 x 90 mg tablets and 21 x 180 mg tablets. Brigatinib tablets are otherwise supplied in aclar/foil blister cards of 7 or 14 tablets each, and packaged in cartons containing 28 tablets each.³

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

Oral:^{3,4,9} BC Cancer usual dose noted in ***bold, italics***
Starting dose = 90 mg (range 60-90 mg) ***PO once daily for 7 days***;
 If tolerated, **increase dose to 180 mg** (range 60-180 mg) ***PO once daily*** thereafter.

For treatment interruptions of 14 days or longer (for reasons other than adverse reactions), resume treatment at the starting dose of 90 mg PO once daily for 7 days before increasing to the previously tolerated dose.

Administer with food or on an empty stomach.
 Do not take with grapefruit or grapefruit juice.

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

Dosage in renal failure:^{3,4}

Creatinine clearance (mL/min)	Dose
≥30	100%
<30	reduce dose from 180 mg to 90 mg (by ~50%) or from 90 mg to 60 mg (by ~30%)

calculated creatinine clearance = $\frac{N \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure:^{3,4} mild or moderate impairment (Child-Pugh A or B): no adjustment required
 severe impairment (Child-Pugh C): reduce dose by ~30% (i.e., from 180 mg to 120 mg, 120 mg to 90 mg, or 90 mg to 60 mg)

Dosage in dialysis: no information found

Children: safety and efficacy not established

REFERENCES:

1. Lexi-Drugs® - Lexicomp Online (database on the Internet). Brigatinib. Wolters Kluwer Clinical Drug Information Inc., 2021. Available at: <http://online.lexi.com>. Accessed 20 June, 2021
2. AHFS Drug Information® - Lexicomp Online (database on the Internet). Brigatinib. Wolters Kluwer Clinical Drug Information Inc., 2021. Available at: <http://online.lexi.com>. Accessed 20 June, 2021
3. Takeda Canada Inc. ALUNBRIG® product monograph. Toronto, Ontario; 2 Mar 2021
4. Takeda Pharmaceutical Company Limited. ALUNBRIG® full prescribing information. Cambridge, MA, USA; May 2020
5. Sophie Sun MD. BC Cancer Lung Tumour Group. Personal Communication. November 1, 2021
6. BC Cancer. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; 1 July 2020
7. Takeda Pharmaceuticals America Inc. ALUNBRIG® full prescribing information. Lexington, MA, USA; February 2022
8. Takeda Pharmaceuticals America Inc. ALUNBRIG® full prescribing information. Lexington, MA, USA; September 2021
9. BC Cancer Lung Tumour Group. (LUAVBRI) BC Cancer Protocol Summary for First-Line Treatment of ALK-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Brigatinib. Vancouver, British Columbia: BC Cancer; June 1, 2022