Drug Monograph

A - Drug Name

brigatinib

COMMON TRADE NAME(S): Alunbrig®

back to top

B - Mechanism of Action and Pharmacokinetics

Brigatinib is an inhibitor of multiple tyrosine kinases including anaplastic lymphoma kinase (ALK), ROS-1 and insulin-like growth factor receptor-1 (IGFR-1). Brigatinib has activity against cells expressing EML4-ALK and 17 mutant forms (including G1202R and L1196M) associated with ALK inhibitor resistance.

Absorption	Effects with food	Co-administration with a high-fat meal led to a 13% reduction in Cmax with no effect on AUC relative to fasted conditions.
	Peak plasma levels	1 to 4 hours
Distribution	PPB	91% plasma proteins
	Cross blood brain barrier?	Not established
Metabolism	Active metabolites	Yes
Elimination	Feces	65%; 41% as unchanged drug
	Urine	25%; 86% as unchanged drug
	Half-life	25 hours

back to top

C - Indications and Status

Health Canada Approvals:

- Non-small cell lung cancer (NSCLC)

(Includes conditional approvals)
Refer to the product monograph for a full list and details of approved indications.

back to top

D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following table lists adverse effects that occurred in ≥2% of patients in a phase III study with advanced ALK-positive NSCLC who received brigatinib 180mg once daily (with an initial 7-day lead-in period at 90mg) or crizotinib. Severe adverse events from other studies or post-marketing are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Bradycardia (12%)	E
	Hypertension (32%) (13% severe)	E
	QT interval prolonged (5%)	E
	Venous thromboembolism (2%)	E
Dermatological	Photosensitivity (4%)	E
	Rash, pruritus (40%) (including dry skin) (3% severe)	E
Gastrointestinal	Abdominal pain (24%)	E
	Anorexia (9%)	E
	Constipation (18%)	E
	Diarrhea (52%) (2% severe)	E
	Dry mouth (5%)	E
	Dyspepsia (8%)	E

	Mucositis (13%)	E
	Nausea, vomiting (30%)	E
General	Edema (18%)	E
	Fatigue (32%)	E
	Fever (19%)	E
Hepatobiliary	↑ Amylase / lipase (57%) (17% severe)	E D
	↑ LFTs (71%) (5% severe)	E
	Other - ↑ Blood LDH, GGT (4%)	E
Metabolic / Endocrine	↑ Cholesterol (3%)	E
	Hyperglycemia (55%) (7% severe)	E
Musculoskeletal	Musculoskeletal pain (28%)	E
	↑CPK (75%) (22% severe)	D
Nervous System	Depression (3%)	E
	Dysgeusia (3%)	E
	Headache (22%)	E
	Insomnia (8%)	E
	Peripheral neuropathy (11%)	E
Ophthalmic	Visual disorders (7%)	E
Renal	Creatinine increased (36%)	E
Respiratory	Cough, dyspnea (35%)	E
	Dysphonia (6%)	E
	Interstitial lung disease (5%)	I E D

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for brigatinib include ↑CPK, ↑ LFTs, ↑ amylase / lipase, hyperglycemia, diarrhea, rash, pruritus, cough, dyspnea, fatigue, hypertension, nausea and vomiting.

Severe, life-threatening, or fatal adverse pulmonary reactions including **interstitial lung disease (ILD)/pneumonitis** have been reported. Most pulmonary adverse reactions were observed within the first 7 days of treatment initiation (or re-initiation, following a dose interruption), usually within the first 24-48 hours. The etiology of pulmonary adverse reactions is not known. ILD/pneumonitis occurred with a median onset of 2 days; 2% of patients experienced pneumonitis later in treatment (median onset: 150 days).

Mild to moderate **visual disturbances** such as blurred vision, photophobia, photopsia, diplopia, and reduced visual acuity have been reported. 2% of patients reported Grade 3 macular edema and cataract.

Elevations of **amylase and lipase** were reported in patients receiving brigatinib but were not associated with clinical pancreatitis.

New or worsening **hyperglycemia** have been reported, including grade 3 toxicity. Some patients with diabetes or glucose intolerance (at baseline) required insulin therapy while receiving brigatinib.

back to top

E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Patients must have a documented ALK-positive status based on a validated assay.

Blood pressure should be controlled prior to initiating brigatinib therapy.

Adults:

Oral: 90mg Daily for the first 7 days; then if tolerated; increase to 180mg Daily

If therapy is interrupted for ≥14 days due to reasons **other than toxicity,** resume treatment at 90mg once daily for 7 days before escalating dose to the previously tolerated dose.

If dose is reduced **for toxicity**, do not subsequently escalate the dose.

See Interactions section for dosing recommendations when administered with CYP3A4 inhibitors/inducers.

Dosage with Toxicity:

Dose Level	Initial Brigatinib Dose (first 7 days) (mg/day)	Maintenance Brigatinib Dose (mg/day)
0	90	180
-1	60	120
-2	Discontinue	90
-3	N/A	60
-4	N/A	Discontinue

Toxicity	Severity	Action
Interstitial Lung Disease (ILD) /Pneumonitis	Grade 1	Hold until recovery to baseline; resume at same dose level. (if WITHIN first 7 days: Do not escalate to 180 mg.) If recurs, discontinue.
	Grade 2	Hold until recovery to baseline; resume at 1 dose level ↓. (if WITHIN first 7 days: Do not escalate to 180 mg.) If recurs, discontinue.
	≥ Grade 3	Discontinue.
Hypertension	Grade 3	Hold until recovery to ≤ grade 1; resume at same dose level. If recurs, hold until recovery to ≤ grade1; resume at 1 dose level ↓ **or** discontinue.
	Grade 4	Hold until recovery to ≤ grade 1; resume at 1 dose level ↓ **or** discontinue. If recurs, discontinue.
Bradycardia (HR <60 bpm)	Symptomatic	Hold until recovery to asymptomatic or resting heart rate ≥60 bpm. If contributing medication identified and discontinued (or dose-adjusted), resume at same dose. If no contributing medication identified (or cannot be discontinued or dose-adjusted), resume at 1 dose level ↓.
	Life-threatening (urgent intervention indicated)	Hold until recovery to asymptomatic or resting heart rate ≥60 bpm. If contributing medication identified and discontinued (or dose-adjusted), resume at 1 dose level ↓. If no contributing medication identified, discontinue. If recurs, discontinue.

Visual Disturbance	Grade 2-3	Hold until recovery to ≤ grade 1 or baseline; resume at 1 dose level ↓.
	Grade 4	Discontinue.
Creatine Phosphokinase (CPK) Elevation	≥Grade 3 with ≥grade 2 muscle pain or weakness	Hold until recovery to ≤ grade 1 or baseline; resume at same dose level. If recurs, hold until recovery to ≤ grade 1 or baseline; resume at 1 dose level ↓.
Lipase/Amylase Elevation	Grade 3	Hold until recovery to ≤ grade 1 or baseline; resume at same dose.
	Recurrent Grade 3 or grade 4	Hold until recovery to ≤ grade 1 or baseline; resume at 1 dose level ↓.
Hyperglycemia	Blood glucose >13.9 mmol/L	Hold until adequate hyperglycemic control; resume at 1 dose level ↓ **or** discontinue.
Elevation of hepatic enzymes	≥Grade 3 AST/ALT with bilirubin ≤2 × ULN	Hold until recovery to ≤3 x ULN or baseline; resume at 1 dose level ↓.
	≥Grade 2 AST/ALT with bilirubin >2 × ULN in the absence of cholestasis or hemolysis	Discontinue.
Other Toxicities	Grade 3	Hold until recovery to baseline; resume at same dose level. If recurs, hold until recovery to baseline; resume at 1 dose level ↓ **or** discontinue.
	Grade 4	Hold until recovery to baseline; resume at 1 dose level ↓. If recurs, hold until recovery to baseline; resume at 1 dose level ↓ **or** discontinue.

Dosage with Hepatic Impairment:

Hepatic Impairment	Brigatinib Dose (mg/day)
Mild or moderate (Child-Pugh class A or B)	No dose adjustment required
Severe (Child-Pugh class C)	Reduce dose by 1 dose level

Dosage with Renal Impairment:

Renal Impairment	Brigatinib Dose (mg/day)
Mild or moderate (CrCl ≥30 mL/min)	No dose adjustment required
Severe (CrCl <30 mL/min)	For 180mg dose: Reduce by 2 dose levels For 90mg dose: Reduce by 1 dose level

Dosage in the elderly:

No dosage adjustment is required. Use brigatinib with caution in elderly patients, especially patients > 85 years of age as there is no available data on patients in this age group. Increased age (≥ 65 years of age) was associated with an increased risk of early pulmonary adverse reactions.

Dosage based on gender:

No dose adjustment required. Population pharmacokinetic analyses showed that gender had no clinically meaningful effect on the pharmacokinetics of brigatinib.

Dosage based on ethnicity:

No dose adjustment required. Population pharmacokinetic analyses showed that race had no clinically meaningful effect on the pharmacokinetics of brigatinib.

Children:

Safety and efficacy in children have not been established.

back to top

F - Administration Guidelines

- Administer with or without food.
- Tablets should be swallowed whole; do not crush or chew.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- If a dose is missed or vomiting occurs after taking a dose, an additional dose should not be given; administer the next dose at the regularly scheduled time.
- Store at 15°C to 30°C

back to top

G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any components of the formulation.

Other Warnings/Precautions:

- Caution in patients with bradycardia (<60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, congestive heart failure or on medications leading to bradycardia.
- Patients with a history of ILD or drug-induced pneumonitis were excluded from clinical trial.
- Brigatinib contains lactose; carefully consider use in patients with lactose intolerance, hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.
- Patients should avoid prolonged sun exposure while taking brigatinib and for at least 5 days after treatment discontinuation. A broad-spectrum UVA/UVB sun screen and lip balm (SPF ≥30) should be used.
- Caution with driving or using machinery as visual disturbances, dizziness, and fatigue may occur with treatment.

Other Drug Properties:

- Carcinogenicity: Unknown
  In vitro and in vivo studies demonstrated that brigatinib is aneugenic.

Pregnancy and Lactation:

- Mutagenicity: No
- Genotoxicity: No
- Embryotoxicity: Probable
- Pregnancy:
  Brigatinib is not recommended for use in pregnancy. Adequate contraception (non-hormonal) should be used by patients and their partners during treatment, and for at least **4 months** after the last dose.
  Hormonal contraceptives may not be effective during brigatinib treatment (See Interactions section).
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended during treatment and for at least **1 week** after the last dose.
- Fertility effects: Probable
  Documented in animal studies with male animals

back to top

H - Interactions

Brigatinib is primarily metabolized by CYP2C8 and CYP3A4. It is also a weak CYP3A4 inducer.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, ritonavir, cobicistat)	↑ brigatinib concentration and/or toxicity (↑ Cmax by 21% and ↑ AUC by 101% with itraconazole)	↓ metabolism of brigatinib	Avoid co-administration. If concomitant use cannot be avoided, reduce brigatinib dose from 180mg to 90mg, or from 90mg to 60mg. After discontinuation of strong CYP3A inhibitor, resume brigatinib at dose that was tolerated prior to the initiation of the CYP3A inhibitor.
Moderate CYP3A inhibitor (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil)	↑ brigatinib concentration and/or toxicity (↑ AUC by ~40% based on PK model)	↓ metabolism of brigatinib	Avoid co-administration. If concomitant use cannot be avoided, reduce brigatinib dose from 180mg to 120mg, from 120mg to 90mg, or from 90mg to 60mg. After discontinuation of CYP3A inhibitor, resume brigatinib at dose that was tolerated prior to the initiation of the CYP3A inhibitor.
Strong CYP3A inducers (e.g., phenytoin, rifabutin, rifampin, carbamazepine, phenobarbital, St. John's Wort, etc.)	↓ brigatinib concentration and/or efficacy (↓ Cmax by 60% and ↓ AUC by 80% with rifampin)	↑ metabolism of brigatinib	Avoid co-administration
Moderate CYP3A inducers (e.g., bosentan, efavirenz,	↓ brigatinib concentration and/or efficacy (↓ AUC by ~50% based on PK model)	↑ metabolism of brigatinib	Avoid co-administration. If concomitant use cannot be avoided,

etravirine, modafinil, etc.)			increase brigatinib dose as follows: After 7 days at current tolerated dose, increase brigatinib dose in 30mg increments, up to a maximum of 2x the brigatinib dose that was tolerated prior to start of inducer. After discontinuation of the CYP3A inducer, resume brigatinib at the dose that was tolerated prior to the initiation of the CYP3A inducer.
Sensitive CYP3A substrates (e.g. cyclosporine, pimozide, sirolimus, tacrolimus, ergot alkaloids, fentanyl, quetiapine, simvastatin)	↓ substrate concentration and/or efficacy	↑ metabolism of substrate	Caution and monitor with drugs with narrow therapeutic index.
Substrates of pregnane X receptor (PXR) inducible enzymes and transporters (e.g., CYP2C, P-gp)	↓ substrate concentration and/or efficacy (theoretical)	Brigatinib induces PXR inducible enzymes and transporters	Caution and monitor with drugs with narrow therapeutic index.
Substrates of P-gp, BCRP, OCT1, MATE1, and MATE2K (e.g., digoxin, dabigatran, colchicine, pravastatin, methotrexate, rosuvastatin, sulfasalazine, metformin)	↑ substrate concentration and/or toxicity	Brigatinib is an inhibitor of P-gp, BCRP, OCT1, MATE1, and MATE2K in vitro.	Caution and monitor with drugs with narrow therapeutic index.

Agents that decrease heart rate (e.g., antiarrhythmics, beta adrenoceptor antagonists, non-dihydropyridine calcium channel blockers, digitalis glycosides, cholinesterase inhibitors, sphingosine-1 phosphate receptor modulators, HIV protease inhibitors, alpha2-adrenoceptor agonists, etc.)	↑ risk of bradycardia	additive	Avoid to the extent possible. If concomitant use cannot be avoided, monitor heart rate more frequently.
Hormonal contraceptives	May ↓ efficacy of hormonal contraceptives	↑ metabolism of hormonal contraceptives	Caution; Use non-hormonal methods of contraception (see Pregnancy and Lactation section)

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Heart rate and blood pressure	Baseline, after 2 weeks and at least monthly during treatment; more frequently in patients receiving medications known to cause bradycardia.
Liver function tests	Baseline, every 2 weeks for the first 3 months of treatment then as clinically indicated
Lipase, amylase, CPK, fasting serum glucose	Baseline, regularly and as clinically indicated
Clinical toxicity assessment for fatigue, visual disturbances, pulmonary, dermatological, GI and musculoskeletal effects	At one week (pulmonary) and at each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- brigatinib - For the treatment of anaplastic lymphoma kinase-positive locally advanced or metastatic non-small cell lung cancer according to clinical criteria

back to top

K - References

Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK inhibitor-naive advanced ALK-positive NSCLC: final results of phase 3 ALTA-1L trial. J Thorac Oncol 2021 Dec;16(12):2091-108.

Camidge DR, Kim HR, Ahn MJ. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. N Engl J Med 2018 Nov 22;379(21):2027-39.

Kim D, Tiseo M, Ahn M, et al. Brigatinib in patients With crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. J Clin Oncol 2017; 35:2490-2498.

Prescribing Information: Alunbrig® (brigatinib). Takeda Pharmaceuticals America, Inc. Lexington, MA. February 2022.

Product Monograph: Alunbrig® (brigatinib). Takeda Canada Inc. July 2022.

July 2024 Updated Interactions and Pregnancy/Lactation sections.

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary's content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person's use of the information in the Formulary.

back to top