NICE RECOMMENDED

ALUNBRIG (brigatinib) is recommended, within its marketing authorisation, for treating anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) in adults who have already had crizotinib.[1]

Takeda ONCOLOGY

ALUNBRIG®

BRIGATINIB

180mg | 90mg | 30mg

TABLETS

MANAGING DOSE MODIFICATIONS WITH ALUNBRIG

A GUIDE FOR HEALTHCARE PROFESSIONALS

ALUNBRIG is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (aNSCLC) previously treated with crizotinib.[2]

Please refer to the Summary of Product Characteristics for full prescribing and monitoring guidance.[2]

For more information, please visit www.ALUNBRIG.co.uk

UK/BRIG/1810/0038a Date of preparation: February 2019

ALUNBRIG - AN EFFECTIVE ONCE-DAILY TREATMENT OPTION IN ALK+ aNSCLC POST CRIZOTINIB

Exceeds 1 year median PFS[a] in ALK+ aNSCLC patients post crizotinib[2]

- Systemic ORR[b] of **56%** (97.5% CI 45–67) of patients[3]
- Systemic mPFS[c] of **16.7 months** (95% CI 11.6–21.4)[3]
- mOS of **34.1 months** (95% CI 27.7–NR)[3]

Effective in the CNS

- Intracranial mPFS[c,d] of **18.4 months** (95% CI 12.6–23.9) in patients with any brain metastases at baseline[3-6]
- Intracranial mDOR[c] of **16.6 months** (95% CI 3.7–NR) in patients with measurable brain metastases at baseline[3-6]

A generally manageable tolerability profile

- The most common[e] treatment-emergent adverse events are **diarrhoea, nausea, cough and increased blood creatine phosphokinase**,[7] which can be managed by dose modification/ interruption[2]

Once-daily dosing

- The convenience of **a single tablet, once daily**[f], that can be taken with or without food[2]
- Treatment should be commenced at the 90 mg dose and if tolerated increased to 180 mg after 7 days[2]

[a]IRC and investigator assessed.
[b]Investigator assessed.
[c]IRC assessed.
[d]Intracranial PFS does not include systemic (non-cranial) disease progression events.
[e]Occurred in ≥10% of patients at a frequency of ≥30% at any grade.
[f]180 mg once daily with a 7-day-lead-in at 90 mg once daily.

Contents

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BRIGATINIB
180mg | 90mg | 30mg
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ALUNBRIG IS THE ONLY APPROVED ALK INHIBITOR WITH A ONE-TABLET, ONCE-DAILY DOSING REGIMEN THAT CAN BE TAKEN WITH OR WITHOUT FOOD[2]

WEEK 1
DAYS 1-7

90 MG ONCE DAILY

IF TOLERATED

WEEK 2+
DAY 8 AND BEYOND

180 MG ONCE DAILY

- Crizotinib should be discontinued **at least 7 days** before initiating ALUNBRIG, as shorter washout periods have been associated with an increased incidence of pulmonary adverse events[2,7]
- The recommended starting dose of ALUNBRIG is **90 mg** once daily for the first 7 days, then if tolerated increased to **180 mg** once daily[2]
- A reduced starting dose of **60 mg** once daily for the first 7 days, then **120 mg** once daily is recommended for patients with **severe hepatic impairment** (Child-Pugh class C)[2]
- A reduced starting dose of **60 mg** once daily for the first 7 days, then **90 mg** once daily is recommended for patients with **severe renal impairment** (eGFR < 30ml/min)[2]

- **If ALUNBRIG is interrupted** for 14 days or longer for reasons other than adverse reactions, treatment should be resumed at **90 mg** once daily for 7 days before increasing to the previously tolerated dose[2]
- If a dose is missed or vomiting occurs after taking a dose, an additional dose should **not** be administered and the next dose should be taken at the scheduled time[2]
- Treatment should continue **as long as clinical benefit is observed[2]**

ALUNBRIG is available in 180 mg, 90 mg and 30 mg tablets

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ALUNBRIG
RECOMMENDED DOSE MODIFICATIONS FOR ADVERSE REACTIONS[2]

FOR **90 MG** ONCE DAILY (RECOMMENDED STARTING DOSE)	
1st	Reduce to 60 mg once daily
2nd	Permanently discontinue

- If patients cannot tolerate the 60 mg once-daily dose, **discontinue** ALUNBRIG permanently[2]

FOR **180 MG** ONCE DAILY	
1st	Reduce to 120 mg once daily
2nd	Reduce to 90 mg once daily
3rd	Reduce to 60 mg once daily

- If patients cannot tolerate the 60 mg once daily dose, **discontinue** ALUNBRIG permanently[2]

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Grade 1

DOSE MODIFICATION

- If event occurs during the first 7 days of treatment, ALUNBRIG should be withheld until recovery to baseline, then resumed at same dose level and not escalated to 180 mg once daily
- If ILD/pneumonitis occurs after the first 7 days of treatment, ALUNBRIG should be withheld until recovery to baseline, then resumed at same dose level
- If ILD/pneumonitis recurs, ALUNBRIG should be permanently discontinued

Grade 2

DOSE MODIFICATION

- If ILD/pneumonitis occurs during the first 7 days of treatment, ALUNBRIG should be withheld until recovery to baseline, then resumed at next lower dose level* and not escalated to 180 mg once daily
- If ILD/pneumonitis occurs after the first 7 days of treatment, ALUNBRIG should be withheld until recovery to baseline. ALUNBRIG should be resumed at next lower dose level*
- If ILD/pneumonitis recurs, ALUNBRIG should be permanently discontinued

Grade 3 or 4

DOSE MODIFICATION

- ALUNBRIG should be permanently discontinued

Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4)

*Please see pages 6-7 for dose modification information

Grade 3

hypertension (SBP ≥160 mmHg or DBP ≥100 mmHg, medical intervention indicated, more than one anti-hypertensive medicinal product, or more intensive therapy than previously used indicated)

DOSE MODIFICATION

- ALUNBRIG should be withheld until hypertension has recovered to Grade ≤1 (SBP <140 mmHg and DBP <90 mmHg), then resumed at same dose
- If Grade 3 hypertension recurs, ALUNBRIG should be withheld until hypertension has recovered to Grade ≤1 then resumed at the next lower dose level* or permanently discontinued

Grade 4

hypertension (life-threatening consequences, urgent intervention indicated)

DOSE MODIFICATION

- ALUNBRIG should be withheld until hypertension has recovered to Grade ≤1 (SBP <140 mmHg and DBP <90 mmHg), then resumed at the next lower dose level* or permanently discontinued
- If Grade 4 hypertension recurs, ALUNBRIG should be permanently discontinued

*Please see pages 6-7 for dose modification information

BRADYCARDIA (HR <60 BPM)

Symptomatic bradycardia

DOSE MODIFICATION

- ALUNBRIG should be withheld until recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above
- If a concomitant medicinal product known to cause bradycardia is identified and discontinued, or its dose is adjusted, ALUNBRIG should be resumed at same dose upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above
- If no concomitant medicinal product known to cause bradycardia is identified, or if contributing concomitant medications are not discontinued or dose modified, ALUNBRIG should be resumed at the next lower dose level* upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above

Bradycardia with life-threatening consequences, urgent intervention indicated

DOSE MODIFICATION

- If contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, ALUNBRIG should be resumed at the next lower dose level* upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above, with frequent monitoring as clinically indicated
- ALUNBRIG should be permanently discontinued if no contributing concomitant medicinal product is identified.
- ALUNBRIG should be permanently discontinued in case of recurrence

Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4)

*Please see pages 6-7 for dose modification information

ELEVATION OF CPK

Grade 3
elevation of CPK (>5.0 × ULN)

DOSE MODIFICATION

- ALUNBRIG should be withheld until recovery to Grade ≤1 (≤2.5 × ULN) or to baseline, then resumed at the same dose
- If Grade 3 elevation of CPK recurs, ALUNBRIG should be withheld until recovery to Grade ≤1 (≤2.5 × ULN) or to baseline, then resumed at the next lower dose level*

Grade 4
elevation of CPK (>10.0 × ULN)

DOSE MODIFICATION

- ALUNBRIG should be withheld until recovery to Grade ≤1 (≤2.5 × ULN) or to baseline, then resumed at the next lower dose level*

ELEVATION OF LIPASE OR AMYLASE

Grade 3
elevation of lipase or amylase (>2.0 × ULN)

DOSE MODIFICATION

- ALUNBRIG should be withheld until recovery to Grade ≤1 (≤1.5 × ULN) or to baseline, then resumed at same dose.
- If Grade 3 elevation of lipase and amylase recurs, ALUNBRIG should be withheld until recovery to Grade ≤1 (≤1.5 × ULN) or to baseline, then resumed at the next lower dose level*

Grade 4
elevation of lipase or amylase (>5.0 × ULN)

DOSE MODIFICATION

- ALUNBRIG should be withheld until recovery to Grade ≤1 (≤1.5 × ULN), then resumed at the next lower dose level*

HEPATOTOXICITY

Grade ≥3 elevation (>5.0 × ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with bilirubin ≤2 × ULN

DOSE MODIFICATION

- ALUNBRIG should be witheld until recovery to baseline or ≥3 × ULN, then resumed at next lower dose level*

Grade ≥2 elevation (>3 × ULN) of ALT or AST with concurrent total bilirubin elevation >2 × ULN in the absence of cholestasis or haemolysis

DOSE MODIFICATION

- ALUNBRIG should be permanently discontinued

HYPERGLYCAEMIA

For Grade 3 (>250 mg/dL or 13.9 mmol/L) or greater

DOSE MODIFICATION

- If adequate hyperglycaemic control cannot be achieved with optimal medical management, ALUNBRIG should be withheld until adequate hyperglycaemic control is achieved. Upon recovery, ALUNBRIG may either be resumed at the next lower dose level* or permanently discontinued

Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4)

*Please see pages 6-7 for dose modification information

VISUAL DISTURBANCE

Grade 2 or 3

DOSE MODIFICATION

- ALUNBRIG should be withheld until recovery to Grade 1 or baseline, then resumed at the next lower dose level*

Grade 4

DOSE MODIFICATION

- ALUNBRIG should be permanently discontinued

OTHER ADVERSE REACTIONS

Grade 3

DOSE MODIFICATION

- ALUNBRIG should be withheld until recovery to baseline, then resumed at the same dose level
- If the Grade 3 event recurs, ALUNBRIG should be withheld until recovery to baseline, then resumed at the next lower dose level* or permanently discontinued

Grade 4

DOSE MODIFICATION

- ALUNBRIG should be withheld until recovery to baseline, then resumed at the next lower dose level*
- If the Grade 4 event recurs, ALUNBRIG should be withheld until recovery to baseline, then resumed at the next lower dose level* or permanently discontinued

*Please see pages 6-7 for dose modification information

ALUNBRIG®▼ (brigatinib) PRESCRIBING INFORMATION

Refer to the Summary of Product Characteristics (SmPC) before prescribing. **Presentation:** Brigatinib 180 mg, 90 mg and 30 mg film-coated tablets. **Indication:** As monotherapy for the treatment of adult patients with anaplastic lymphoma kinase-positive advanced non-small cell lung cancer previously treated with crizotinib. **Dosage & Administration:** Recommended starting dose is 90 mg once daily for the first 7 days, then 180 mg once daily. If Alunbrig is interrupted for 14 days or longer for reasons other than adverse reactions, treatment should be resumed at 90 mg once daily for 7 days before increasing to the previously tolerated dose. If a dose is missed or vomiting occurs after taking a dose, an additional dose should not be administered and the next dose should be taken at the scheduled time. Treatment should continue as long as clinical benefit is observed. Dosing interruption and/or dose reduction may be required. See SmPC for full dosage information and dose modifications. Paediatric populations: No data are available. Elderly patients: Dose adjustment is not required in elderly patients. No available data on patients aged > 85 years. Hepatic impairment: A reduced starting dose of 60 mg once daily for the first 7 days, then 120 mg once daily is recommended for patients with severe hepatic impairment (Child-Pugh class C). Renal impairment: A reduced starting dose of 60 mg once daily for the first 7 days, then 90 mg once daily is recommended for patients with severe renal impairment (eGFR < 30 mL/min). Patients with severe renal impairment should be closely monitored for new or worsening respiratory symptoms (e.g., dyspnoea, cough, etc.). **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and Precautions:** See SmPC for recommended dose modifications. Pulmonary adverse reactions: Patients should be monitored for new or worsening respiratory symptoms (e.g., dyspnoea, cough, etc.), particularly in the first week of treatment. If pneumonitis is suspected, the dose of Alunbrig should be withheld, and the patient evaluated for other causes of symptoms (e.g., pulmonary embolism, tumour progression, and infectious pneumonia). Dose modification may be required; Hypertension: Heart rate and blood pressure should be monitored regularly. Withhold Alunbrig in patients with severe hypertension (≥ Grade 3) until hypertension has recovered to Grade 1 or to baseline. Modify dose accordingly; Bradycardia: Caution should be exercised when administering Alunbrig in combination with other agents known to cause bradycardia. If symptomatic bradycardia occurs, treatment with Alunbrig should be withheld and concomitant medicinal products known to cause bradycardia should be evaluated. Upon recovery, the dose should be modified according to SmPC. In case of life-threatening bradycardia, if no contributing concomitant medication is identified or in case of recurrence, treatment with Alunbrig should be discontinued; Visual disturbance: Advise patients to report any visual symptoms. Consider ophthalmologic evaluation / dose reduction for new or worsening severe symptoms. Creatine phosphokinase (CPK) elevation: Patients should be advised to report any unexplained muscle pain, tenderness, or weakness. CPK levels should be monitored regularly during Alunbrig treatment. Based on the severity of the CPK elevation, treatment with Alunbrig should be withheld, and the dose modified. Elevations of pancreatic enzymes: Lipase and amylase should be monitored regularly during treatment with Alunbrig. Based on the severity of the laboratory abnormalities, treatment with Alunbrig should be withheld, and the dose modified. Hepatotoxicity: Liver function, including AST, ALT and total bilirubin should be assessed prior to the initiation of Alunbrig and then every 2 weeks during the first 3 months of treatment. Thereafter, monitoring should be performed periodically. Based on the severity of the laboratory abnormalities, treatment should be withheld, and the dose modified. Hyperglycaemia: Fasting serum glucose should be assessed prior to initiation of Alunbrig and monitored periodically thereafter. Antihyperglycaemic medications should be initiated or optimised as needed. If adequate hyperglycaemic control cannot be achieved with optimal medical management, Alunbrig should be withheld until adequate hyperglycaemic control is achieved; upon recovery, dose reduce Alunbrig as per the SmPC or permanent discontinuation may be considered; Lactose: Alunbrig contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take Alunbrig. **Interactions:** Avoid use with strong CYP3A inhibitors. See SmPC for dosage modifications for Alunbrig if concomitant use with a strong CYP3A inhibitor cannot be avoided. Strong and moderate CYP3A inducers should be avoided. Grapefruit or grapefruit juice should be avoided. Coadministration of Alunbrig with CYP3A substrates with a narrow therapeutic index should be avoided as Alunbrig may reduce their effectiveness. Co-administration of Alunbrig with substrates of P-gp, BCRP, organic cation transporter 1, multidrug and toxin extrusion protein (MATE) 1 and 2K may increase their plasma concentrations. Patients should be closely monitored when Alunbrig is co-administered with substrates of these transporters with a narrow therapeutic index. **Fertility, Pregnancy and Lactation:** Women of reproductive potential should be advised not to become pregnant and to use effective non-hormonal contraception during treatment with Alunbrig and for at least 4 months following the final dose. Men should be advised not to father a child during Alunbrig treatment. Men with female partners of reproductive potential should be advised to use effective contraception during and for at least 3 months after the last Alunbrig treatment. No clinical data on the use of Alunbrig in pregnant women. Alunbrig should not be used during pregnancy unless the clinical condition of the mother requires treatment. Breast-feeding should be stopped during treatment with Alunbrig. No human data are available on the effect of Alunbrig on fertility. **Undesirable Effects:** Very common (≥1/10): Pneumonia, upper respiratory tract infection, anaemia, lymphocyte count decreased, APTT increased, white blood cell count decreased, neutrophil count decreased, decreased platelet count, hyperglycaemia, hyperinsulinaemia, hypophosphataemia, decreased appetite, hypokalaemia, hypomagnesaemia, hyponatraemia, hypercalcaemia, insomnia, headache, peripheral neuropathy, dizziness, visual disturbance, hypertension, cough, dyspnoea, lipase increased, nausea, diarrhoea, amylase increased, vomiting, constipation, abdominal pain, dry mouth, stomatitis, AST increased, ALT increased, alkaline phosphatase increased, rash, pruritus, blood CPK increased, myalgia, arthralgia, musculoskeletal chest pain, blood creatinine increased, fatigue, oedema, pyrexia. Common (≥1/100 to <1/10): Memory impairment, dysgeusia, tachycardia, electrocardiogram QT prolonged, bradycardia, palpitations, pneumonitis, dyspepsia, flatulence, blood lactate dehydrogenase increased, hyperbilirubinaemia, dry skin, photosensitivity reaction, pain in extremity, musculoskeletal stiffness, pain, non-cardiac chest pain, chest discomfort, weight decreased. Other serious uncommon (≥1/1,000 to <1/100) undesirable effects: pancreatitis. **Refer to the SmPC for details on full side effect profile and interactions. Legal Classification:** POM. **UK Basic NHS Price:** 30mg x56: £2,450, 90mg tablets x 28: £3,675, 90mg tablets x 7: £918.75, 180mg tablets x 28: £4,900 **Marketing Authorisation Numbers:** EU/1/18/1264/003, EU/1/18/1264/008, EU/1/18/1264/005, EU/1/18/1264/010 **Additional information is available on request from:** Takeda UK Ltd. Building 3, Glory Park, Glory Park Avenue, Wooburn Green, Buckinghamshire, HP10 0DF. Tel: 01628 537900 Fax: 01628 526617. **PI Approval Code:** UK/BRIG/1810/0036(1) **PI Date of Preparation:** December 2018

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/. Adverse events should also be reported to Takeda UK Ltd 01628-537900

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In general I have found side effects to be manageable using the recommended dose modifications; I found dose reduction an appropriate option to allow my patients who experienced side effects to remain on treatment.

Dr Joanne Evans
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Patients should be provided with a **patient alert card (PAC).** In the first 7 days, they should be closely monitored for adverse reactions, particularly pulmonary adverse reactions, and the dose adjusted or discontinued if necessary.

Please refer to the Summary of Product Characteristics for full prescribing and monitoring guidance.[2]

REFERENCES

1. NICE Final Appraisal Determination: Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib. https://www.nice.org.uk/guidance/gid-ta10268/documents/final-appraisal-determination-document. Accessed February 2019.
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5. Camidge DR, et al. J Clin Oncol 2018;36:2693-701.
6. Ou S-HI, et al. Oral presentation at ESMO 2017, poster 1345P.
7. Kim DW, et al. J Clin Oncol 2017;35:2490–8.

ABBREVIATIONS

ALK, anaplastic lymphoma kinase; **ALT**, alanine aminotransferase; **aNSCLC**, advanced non-small cell lung cancer; **AST**, aspartate aminotransferase; **BPM**, beats per minute; **CI**, confidence interval; **CNS**, central nervous system; **CPK**, creatine phosphokinase; **DBP**, diastolic blood pressure; **eGFR**, estimated glomerular filtration rate; **HR**, heart rate; **ILD**, interstitial lung disease; **IRC**, independent review committee; **mDOR**, median duration of response; **mOS**, median overall survival; **mPFS,** median progression free survival; **NR**, not reached; **ORR**, objective response rate; **PFS**, progression-free survival; **SBP**, systolic blood pressure; **ULN**, upper limit of normal.

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