Brigatinib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
For the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib	C34	00562a	CDS 01/06/2019
Monotherapy for the treatment of adult patients with ALK positive advanced NSCLC previously not treated with an ALK inhibitor	C34	00562b	CDS 01/10/2020

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Brigatinib is administered orally with a starting dose of 90mg once daily for the first 7 days and then increased to 180mg once daily. Treatment should be continued until disease progression or unacceptable toxicity develops.

WEEK	Brigatinib Dose (mg)	Route	Cycle
1	90	PO	Continuously for 7 days
2 onwards	180	PO	Continuous
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.			
The tablets should be swallowed whole with water and may be taken with or without food.			
Grapefruit or grapefruit juice may increase plasma concentrations of brigatinib and should be avoided.			

ELIGIBILITY:

- Indications as above
- ALK-positive NSCLC as demonstrated by an accurate and validated test method
- ECOG 0-2
- Adequate organ function

CAUTION

Use with caution in patients with:

- QT interval corrected (Fridericia) (QTcF) of >450 milliseconds (msec) in males or >470 msec in females

EXCLUSIONS:

- Known or suspected hypersensitivity to brigatinib or its excipients.
- Clinically significant pulmonary interstitial disease or drug-related pneumonitis.
- Clinically significant uncontrolled cardiovascular disease including uncontrolled hypertension or significant bradycardia.

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- ALK-positive NSCLC as demonstrated by an accurate and validated test method
- FBC, renal and liver profile
- Pulmonary function test
- ECG and blood pressure
- Fasting serum glucose, CPK, amylase and/or lipase levels

Regular tests:

- FBC, and renal profile monthly
- ECG and blood pressure every 2 weeks for first cycle and then monthly thereafter or as clinically indicated
- Liver profile every two weeks in the first three months of treatment and then as clinically indicated
- Clinical assessment for early pulmonary symptoms on day 8 and 15 of first treatment cycle and then subsequently monthly or as clinically indicated.
- Fasting serum glucose, CPK, amylase and/or lipase levels monthly

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- If treatment 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.

Table 1: Recommended Dose Reduction Levels of Brigatinib

Dose level 0	Dose Level -1	Dose Level -2	Dose Level -3
90mg (first 7 days)	60mg	Discontinue	N/A
180mg	120mg	90mg	60mg

Note: Brigatinib should be permanently discontinued if patient is unable to tolerate the 60 mg once daily dose.

Haematological:

Table 2: Recommended Dose Modification of Brigatinib for Haematological Toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
0.5-1	and	25-50	Withhold dose until recovery to baseline then resume at the same dose level. If the toxicity reoccurs, withhold dose until recovery to baseline then resume at the next lower dose level as per table 1 or permanently discontinue.
<0.5	and	<25	Withhold dose until recovery to baseline then resume at the next lower dose level as per table 1. If the toxicity reoccurs, withhold dose until recovery to baseline then resume at the next lower dose level as per table 1 or permanently discontinue.

Renal and Hepatic Impairment:

Table 3: Recommended Dose Modification of Brigatinib in Renal and Hepatic Impairment

Renal Impairment		Hepatic Impairment*	
Cr Cl (ml/min)	**Dose**	**Level**	**Dose**
≥ 30	No dose adjustment required	**Mild–moderate (Child- Pugh Class A or B)**	No dose adjustment required
< 30	A reduced starting dose of 60mg once daily for the first 7 days, then 90 mg once daily is recommended	**Severe (Child-Pugh Class C)**	A reduced starting dose of 60 mg once daily for the first 7 days then 120 mg once daily

***See Table 5 for management of treatment-related hepatotoxicity**

Management of adverse events:

Table 4: Recommended Dose Modification of Brigatinib for Adverse Events

Adverse reactions	Dose modification
Interstitial lung disease (ILD)/pneumonitis	
Grade 1 First occurrence • Within first seven days of treatment • After first seven days of treatment Second occurrence	Brigatinib should be withheld until recovery to baseline, then resumed at same dose level and **not** escalated to 180 mg once daily. Brigatinib should be withheld until recovery to baseline, and then resumed at same dose level. Brigatinib should be permanently discontinued.
Grade 2 First occurrence • Within first seven days of treatment • After first seven days of treatment	Brigatinib should be withheld until recovery to baseline, and then resumed at next lower dose level as described in Table 1 and **not** escalated to 180 mg once daily. Brigatinib should be withheld until recovery to baseline and then resumed at next lower dose level as described in Table 1.

Second occurrence	Brigatinib should be permanently discontinued.
Grade 3 or 4	Brigatinib should be permanently discontinued.
Hypertension	
Grade 3 First occurrence Second occurrence	 Brigatinib should be withheld until hypertension has recovered to Grade ≤ 1 (SBP < 140 mmHg and DBP < 90 mmHg), then resumed at same dose. Brigatinib should be withheld until hypertension has recovered to Grade ≤ 1 then resumed at the next lower dose level as per Table 1 or permanently discontinued.
Grade 4 First occurrence Second occurrence	 Brigatinib 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 as per Table 1 or permanently discontinued. Brigatinib should be permanently discontinued.
Bradycardia[a]	
Symptomatic bradycardia	Brigatinib 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, brigatinib 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, brigatinib should be resumed at the next lower dose level as per Table 1 upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above.
Bradycardia with life-threatening consequences, urgent intervention indicated First occurrence Second occurrence	 • If contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, brigatinib should be resumed at the next lower dose level as per Table 1 upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. • Brigatinib should be permanently discontinued if no contributing concomitant medicinal product is identified. Brigatinib should be permanently discontinued in case of recurrence
Elevation of CPK	
Grade 3 or 4 elevation (CPK > 5.0 × ULN) with grade ≥2 muscle pain or weakness	Brigatinib should be withheld until recovery to Grade ≤ 1 (≤ 2.5 × ULN) elevation of CPK or to baseline, then resumed at the same dose. If Grade 3 or 4 elevation of CPK recurs with Grade ≥2 muscle pain or weakness, brigatinib should be withheld until recovery to Grade ≤ 1 (≤ 2.5 × ULN) elevation of CPK or to baseline, then resumed at the next lower dose level as per Table 1.

Elevation of lipase or amylase	
Grade 3 (lipase or amylase > 2.0 × ULN) First occurrence Second occurrence	 Brigatinib 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 or amylase recurs, Brigatinib should be withheld until recovery to Grade ≤ 1 (≤ 1.5 × ULN) or to baseline, then resumed at the next lower dose level as per Table 1.
Grade 4 (lipase or amylase > 5.0 x ULN)	Brigatinib should be withheld until recovery to Grade ≤ 1 (≤ 1.5 × ULN), then resumed at the next lower dose level as per Table 1.
Hyperglycaemia	
Grade 3 (> 250 mg/dL or 13.9 mmol/L) or greater	If adequate hyperglycaemic control cannot be achieved with optimal medical management, brigatinib should be withheld until adequate hyperglycaemic control is achieved. Upon recovery, brigatinib may either be resumed at the next lower dose as per Table 1 or permanently discontinued.
Visual Disturbance	
Grade 2 or 3 **Grade 4**	Brigatinib should be withheld until recovery to Grade 1 or baseline, then resumed at the next lower dose level as per Table 1. Brigatinib should be permanently discontinued.
Other adverse reactions	
Grade 3 First occurrence Second occurrence	 Brigatinib should be withheld until recovery to baseline and then resumed at the same dose level. If the Grade 3 event recurs, brigatinib should be withheld until recovery to baseline and then resumed at the next lower dose level as per Table 1 or permanently discontinued.
Grade 4 First occurrence Second occurrence	 Brigatinib should be withheld until recovery to baseline, then resumed at the next lower dose level as per Table 1. If the Grade 4 event recurs, brigatinib should be withheld until recovery to baseline, then resumed at the next lower dose level as per Table 1 or permanently discontinued.
*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4)	

[a]Heart rate less than 60 beats per minute (bpm).

bpm = beats per minute; CPK = Creatine Phosphokinase; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure; ULN = upper limit of normal

Treatment related hepatotoxicity:

Table 5: Recommended dose modification of brigatinib for treatment-related hepatotoxicity

Bilirubin		AST/ALT	Dose modification
≤ 2 × ULN	**And**	> 5.0 × ULN	Brigatinib should be withheld until recovery to baseline or less than or equal to 3 x ULN then resumed at the next lower dose level as per Table 1.
> 2 × ULN in the absence of cholestasis or haemolysis	And	> 3 × ULN	Brigatinib should be permanently discontinued.

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

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to Low (**Refer to local policy)**

PREMEDICATIONS: Not required

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Brigatinib is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Pulmonary adverse reactions:** Severe, life-threatening, and fatal pulmonary adverse reactions, including those with features consistent with ILD/pneumonitis, can occur in patients treated with brigatinib. Most pulmonary adverse reactions were observed within the first 7 days of treatment. Grade 1-2 pulmonary adverse reactions resolved with interruption of treatment or dose modification. Increased age and shorter interval (less than 7 days) between the last dose of crizotinib and the first dose of brigatinib were independently associated with an increased rate of these pulmonary adverse reactions. These factors should be considered when initiating treatment with brigatinib. Patients with a history of ILD or drug-induced pneumonitis were excluded from the pivotal trials. Some patients experienced pneumonitis later in treatment with brigatinib. Patients should be monitored for new or worsening respiratory symptoms (e.g., dyspnoea, cough, etc.), particularly in the first week of treatment.
- **Hypertension:** Hypertension has occurred in patients treated with brigatinib. Blood pressure should be monitored regularly during treatment with brigatinib. Hypertension should be treated according to standard guidelines to control blood pressure. Heart rate should be monitored more frequently in patients if concomitant use of a medicinal product known to cause bradycardia cannot be avoided. Upon discontinuation of brigatinib, antihypertensive medications may require medical review.
- **Bradycardia:** Bradycardia has occurred in patients treated with brigatinib. Caution should be exercised when administering brigatinib in combination with other agents known to cause bradycardia. Heart rate and blood pressure should be monitored regularly. If bradycardia occurs, refer to Table 4 for management.
- **Visual disturbance:** Visual disturbance adverse reactions have occurred in patients treated with brigatinib. Patients should be advised to report any visual symptoms. For new or worsening severe visual symptoms, an ophthalmologic evaluation and dose reduction should be considered. Caution should be exercised when driving or operating machines.
- **Creatine phosphokinase (CPK) elevation:** Elevations of CPK have occurred in patients treated with brigatinib. Patients should be advised to report any unexplained muscle pain, tenderness, or weakness. CPK levels should be monitored regularly during brigatinib treatment. IF CPK elevation occurs refer to Table 4 for management.
- **Elevations of pancreatic enzymes:** Elevations of amylase and lipase have occurred in patients treated with brigatinib. Lipase and amylase should be monitored regularly during treatment with brigatinib. If elevation of pancreatic enzymes occurs refer to Table 4 for management.

- **Hepatotoxicity:** Elevations of hepatic enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT)) and bilirubin have occurred in patients treated with brigatinib. Liver function, including AST, ALT and total bilirubin should be assessed prior to the initiation of brigatinib and then every 2 weeks during the first 3 months of treatment. Thereafter, monitoring should be performed periodically. If elevations of hepatic enzymes occurs, refer to Table 4 for management.
- **Hyperglycaemia:** Elevations of serum glucose have occurred in patients treated with brigatinib. Fasting serum glucose should be assessed prior to initiation of brigatinib and monitored periodically thereafter. Antihyperglycaemic treatment should be initiated or optimised as needed. If adequate hyperglycaemic control cannot be achieved with optimal medical management, brigatinib should be withheld until adequate hyperglycaemic control is achieved; upon recovery reducing the dose as described in Table 4 may be considered or brigatinib may be permanently discontinued.
- **Fertility:** Women of childbearing potential should be advised to use effective non-hormonal contraception during treatment with brigatinib and for at least 4 months following the final dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment and for at least 3 months after the last dose of brigatinib.
- **Lactose:** Brigatinib contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

DRUG INTERACTIONS:

- **CYP3A inhibitors**: The concomitant use of brigatinib with strong and moderate CYP3A inhibitors should be avoided. If concomitant use of strong CYP3A inhibitors cannot be avoided, the dose of brigatinib should be reduced from 180mg to 90mg or from 90mg to 60mg. After discontinuation of a strong CYP3A inhibitor, brigatinib should be resumed at the dose that was tolerated prior to the initiation of the strong CYP3A inhibitor.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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2. Camidge, D R et al. Brigatinib Versus Crizotinib in Advanced ALK Inhibitor-Naive ALK-Positive Non Small Cell Lung Cancer: Second Term Interim Analysis of the Phase III ALTA 1L Trial. J Clin Oncol 2020 Aug 11;JCO2000505
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
4. Brigatinib (Alunbrig®) Summary of Product characteristics. Accessed Aug 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/alunbrig-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	13/06/2019		Dr Dearbhaile Collins
2	18/09/2020	Addition of 1L indication Elevation of CPK adverse reaction amended	Prof Maccon Keane
3	22/10/2021	Reviewed. Updated treatment table. Amended regular tests (pulmonary). Added to adverse effects.	Prof. Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.