

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Alunbrig 30 mg film-coated tablets
Alunbrig 90 mg film-coated tablets
Alunbrig 180 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Alunbrig 30 mg film-coated tablets

Each film-coated tablet contains 30 mg of brigatinib.

Excipient with known effect

Each film-coated tablet contains 56 mg of lactose monohydrate.

Alunbrig 90 mg film-coated tablets

Each film-coated tablet contains 90 mg of brigatinib.

Excipient with known effect

Each film-coated tablet contains 168 mg of lactose monohydrate.

Alunbrig 180 mg film-coated tablets

Each film-coated tablet contains 180 mg of brigatinib.

Excipient with known effect

Each film-coated tablet contains 336 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Alunbrig 30 mg film-coated tablets

Round, white to off-white film-coated tablet of approximately 7 mm in diameter with debossed “U3” on one side and plain on the other side.

Alunbrig 90 mg film-coated tablets

Oval, white to off-white film-coated tablet of approximately 15 mm in length with debossed “U7” on one side and plain on the other side.

Alunbrig 180 mg film-coated tablets

Oval, white to off-white film-coated tablet of approximately 19 mm in length with debossed “U13” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment with Alunbrig should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

ALK-positive NSCLC status should be known prior to initiation of Alunbrig therapy. A validated ALK assay is necessary for the selection of ALK-positive NSCLC patients (see section 5.1). Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilised.

Posology

The recommended starting dose of Alunbrig 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.

Dose adjustments

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability.

Alunbrig dose modification levels are summarised in Table 1.

Table 1: Recommended Alunbrig dose reduction levels

Dose	Dose reduction levels		
	First	Second	Third
90 mg once daily (first 7 days)	reduce to 60 mg once daily	permanently discontinue	not applicable
180 mg once daily	reduce to 120 mg once daily	reduce to 90 mg once daily	reduce to 60 mg once daily

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

Recommendations for dose modifications of Alunbrig for the management of adverse reactions are summarised in Table 2.

Table 2: Recommended Alunbrig dose modifications for adverse reactions

Adverse reaction	Severity*	Dose modification
Interstitial lung disease (ILD)/pneumonitis	Grade 1	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 as described in Table 1 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 as described in Table 1. • If ILD/pneumonitis recurs, Alunbrig should be permanently discontinued.
	Grade 3 or 4	<ul style="list-style-type: none"> • Alunbrig should be permanently discontinued.
Hypertension	Grade 3 hypertension (SBP \geq 160 mmHg or DBP \geq 100 mmHg, medical intervention indicated, more than one anti-hypertensive medicinal product, or more intensive therapy than previously used indicated)	<ul style="list-style-type: none"> • Alunbrig should be withheld until hypertension has recovered to Grade \leq 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 \leq 1 then resumed at the next lower dose level per Table 1 or permanently discontinued
	Grade 4 hypertension (life threatening consequences, urgent intervention indicated)	<ul style="list-style-type: none"> • Alunbrig should be withheld until hypertension has recovered to Grade \leq 1 (SBP < 140 mmHg and DBP < 90 mmHg), then resumed at the next lower dose level per Table 1 or permanently discontinued. • If Grade 4 hypertension recurs, Alunbrig should be permanently discontinued.
Bradycardia (HR less than 60 bpm)	Symptomatic bradycardia	<ul style="list-style-type: none"> • 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 per Table 1 upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above.

Adverse reaction	Severity*	Dose modification
	Bradycardia with life-threatening consequences, urgent intervention indicated	<ul style="list-style-type: none"> • If contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, Alunbrig should be resumed at the next lower dose level 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. • Alunbrig should be permanently discontinued if no contributing concomitant medicinal product is identified. • Alunbrig should be permanently discontinued in case of recurrence.
Elevation of CPK	Grade 3 elevation of CPK ($> 5.0 \times \text{ULN}$)	<ul style="list-style-type: none"> • Alunbrig should be withheld until recovery to Grade ≤ 1 ($\leq 2.5 \times \text{ULN}$) 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 ($\leq 2.5 \times \text{ULN}$) or to baseline, then resumed at the next lower dose level per Table 1.
	Grade 4 elevation of CPK ($> 10.0 \times \text{ULN}$)	<ul style="list-style-type: none"> • Alunbrig should be withheld until recovery to Grade ≤ 1 ($\leq 2.5 \times \text{ULN}$) or to baseline, then resumed at the next lower dose level per Table 1.
Elevation of lipase or amylase	Grade 3 elevation of lipase or amylase ($> 2.0 \times \text{ULN}$)	<ul style="list-style-type: none"> • Alunbrig should be withheld until recovery to Grade ≤ 1 ($\leq 1.5 \times \text{ULN}$) or to baseline, then resumed at same dose. • If Grade 3 elevation of lipase or amylase recurs, Alunbrig should be withheld until recovery to Grade ≤ 1 ($\leq 1.5 \times \text{ULN}$) or to baseline, then resumed at the next lower dose level per Table 1.
	Grade 4 elevation of lipase or amylase ($> 5.0 \times \text{ULN}$)	<ul style="list-style-type: none"> • Alunbrig should be withheld until recovery to Grade ≤ 1 ($\leq 1.5 \times \text{ULN}$), then resumed at the next lower dose level per Table 1.
Hepatotoxicity	Grade ≥ 3 elevation ($> 5.0 \times \text{ULN}$) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with bilirubin $\leq 2 \times \text{ULN}$	<ul style="list-style-type: none"> • Alunbrig should be withheld until recovery to baseline or less than or equal to $3 \times \text{ULN}$, then resumed at next lower dose per Table 1.
	Grade ≥ 2 elevation ($> 3 \times \text{ULN}$) of ALT or AST with concurrent total bilirubin elevation $> 2 \times \text{ULN}$ in the absence of cholestasis or haemolysis	<ul style="list-style-type: none"> • Alunbrig should be permanently discontinued.
Hyperglycaemia	For Grade 3 (greater than 250 mg/dL or 13.9 mmol/L) or greater	<ul style="list-style-type: none"> • 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 per Table 1 or permanently discontinued.

Adverse reaction	Severity*	Dose modification
Visual Disturbance	Grade 2 or 3	<ul style="list-style-type: none"> Alunbrig should be withheld until recovery to Grade 1 or baseline, then resumed at the next lower dose level per Table 1.
	Grade 4	<ul style="list-style-type: none"> Alunbrig should be permanently discontinued.
Other adverse reactions	Grade 3	<ul style="list-style-type: none"> 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 as per Table 1 or permanently discontinued.
	Grade 4	<ul style="list-style-type: none"> Alunbrig 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, Alunbrig should be withheld until recovery to baseline, then resumed at the next lower dose level as per Table 1 or permanently discontinued.
bpm = beats per minute; CPK = Creatine Phosphokinase; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure; ULN = upper limit of normal		

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

Special populations

Elderly patients

The limited data on the safety and efficacy of Alunbrig in patients aged 65 years and older suggest that a dose adjustment is not required in elderly patients (see section 4.8). There are no available data on patients over 85 years of age.

Hepatic impairment

No dose adjustment of Alunbrig is required for patients with mild hepatic impairment (Child-Pugh class A) or moderate hepatic impairment (Child-Pugh class B). 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) (see section 5.2).

Renal impairment

No dose adjustment of Alunbrig is required for patients with mild or moderate renal impairment (estimated glomerular filtration rate (eGFR) \geq 30 mL/min). 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) (see section 5.2). Patients with severe renal impairment should be closely monitored for new or worsening respiratory symptoms that may indicate ILD/pneumonitis (e.g., dyspnoea, cough, etc.) particularly in the first week (see section 4.4).

Paediatric population

The safety and efficacy of Alunbrig in patients less than 18 years of age have not been established. No data are available.

Method of administration

Alunbrig is for oral use. The tablets should be swallowed whole and with water. Alunbrig may be taken with or without food.

Grapefruit or grapefruit juice may increase plasma concentrations of brigatinib and should be avoided (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 Alunbrig (see section 4.8).

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 Alunbrig were independently associated with an increased rate of these pulmonary adverse reactions. These factors should be considered when initiating treatment with Alunbrig. Patients with a history of ILD or drug-induced pneumonitis were excluded from the pivotal trial.

Some patients experienced pneumonitis later in treatment with Alunbrig.

Patients should be monitored for new or worsening respiratory symptoms (e.g., dyspnoea, cough, etc.), particularly in the first week of treatment. Evidence of pneumonitis in any patient with worsening respiratory symptoms should be promptly investigated. 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). The dose should be modified accordingly (see section 4.2).

Hypertension

Hypertension has occurred in patients treated with Alunbrig (see section 4.8).

Blood pressure should be monitored regularly during treatment with Alunbrig. 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. For severe hypertension (\geq Grade 3), Alunbrig should be withheld until hypertension has recovered to Grade 1 or to baseline. The dose should be modified accordingly (see section 4.2).

Bradycardia

Bradycardia has occurred in patients treated with Alunbrig (see section 4.8). Caution should be exercised when administering Alunbrig in combination with other agents known to cause bradycardia. Heart rate and blood pressure should be monitored regularly.

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 accordingly (see section 4.2). In case of life-threatening bradycardia, if no contributing concomitant medication is identified or in case of recurrence, treatment with Alunbrig should be discontinued (see section 4.2).

Visual disturbance

Visual disturbance adverse reactions have occurred in patients treated with Alunbrig (see section 4.8). 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 (see section 4.2).

Creatine phosphokinase (CPK) elevation

Elevations of CPK have occurred in patients treated with Alunbrig (see section 4.8). 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 accordingly (see section 4.2).

Elevations of pancreatic enzymes

Elevations of amylase and lipase have occurred in patients treated with Alunbrig (see section 4.8). 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 accordingly (see section 4.2).

Hepatotoxicity

Elevations of hepatic enzymes (aspartate aminotransferase, alanine aminotransferase) and bilirubin have occurred in patients treated with Alunbrig (see section 4.8). 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 accordingly (see section 4.2).

Hyperglycaemia

Elevations of serum glucose have occurred in patients treated with Alunbrig. Fasting serum glucose should be assessed prior to initiation of Alunbrig and monitored periodically thereafter. Antihyperglycaemic treatment 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 reducing the dose as described in Table 1 may be considered or Alunbrig may be permanently discontinued.

Drug-drug interactions

The concomitant use of Alunbrig with strong CYP3A inhibitors should be avoided. If concomitant use of strong CYP3A inhibitors cannot be avoided, the dose of Alunbrig should be reduced from 180 mg to 90 mg, or from 90 mg to 60 mg. After discontinuation of a strong CYP3A inhibitor, Alunbrig should be resumed at the dose that was tolerated prior to the initiation of the strong CYP3A inhibitor.

The concomitant use of Alunbrig with strong and moderate CYP3A inducers should be avoided (see section 4.5).

Fertility

Women of childbearing potential should be advised to use effective non-hormonal contraception during treatment with Alunbrig 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 Alunbrig (see section 4.6).

Lactose

Alunbrig contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Agents that may increase brigatinib plasma concentrations

CYP3A inhibitors

In vitro studies demonstrated that brigatinib is a substrate of CYP3A4/5. In healthy subjects, coadministration of multiple 200 mg twice daily doses of itraconazole, a strong CYP3A inhibitor, with a single 90 mg brigatinib dose increased brigatinib C_{max} by 21%, AUC_{0-INF} by 101% (2-fold), and AUC_{0-120} by 82% (< 2-fold), relative to a 90 mg brigatinib dose administered alone. The concomitant use of strong CYP3A inhibitors with Alunbrig, including but not limited to certain antivirals (e.g., indinavir, nelfinavir, ritonavir, saquinavir), macrolide antibiotics (e.g., clarithromycin, telithromycin, troleandomycin), antifungals (e.g., ketoconazole, voriconazole), mibefradil, and nefazodone should be avoided. If concomitant use of strong CYP3A inhibitors cannot be avoided, the dose of Alunbrig should be reduced by approximately 50% (i.e. from 180 mg to 90 mg, or from 90 mg to 60 mg). After

discontinuation of a strong CYP3A inhibitor, Alunbrig should be resumed at the dose that was tolerated prior to the initiation of the strong CYP3A inhibitor.

Moderate CYP3A inhibitors (e.g., diltiazem and verapamil) may increase the AUC of brigatinib by approximately 40% based on simulations from a physiologically-based pharmacokinetic model. No dose adjustment is required for Alunbrig in combination with moderate CYP3A inhibitors. Patients should be closely monitored when Alunbrig is coadministered with moderate CYP3A inhibitors.

Grapefruit or grapefruit juice may also increase plasma concentrations of brigatinib and should be avoided (see section 4.2).

CYP2C8 inhibitors

In vitro studies demonstrated that brigatinib is a substrate of CYP2C8. In healthy subjects, coadministration of multiple 600 mg twice daily doses of gemfibrozil, a strong CYP2C8 inhibitor, with a single 90 mg brigatinib dose reduced brigatinib C_{max} by 41%, AUC_{0-120} by 12%, and AUC_{0-120} by 15%, relative to a 90 mg brigatinib dose administered alone. The effect of gemfibrozil on the pharmacokinetics of brigatinib is not clinically meaningful and the underlying mechanism for the decreased exposure of brigatinib is unknown. No dose adjustment is required during coadministration with strong CYP2C8 inhibitors.

P-gp and BCRP inhibitors

Brigatinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) *in vitro*. Given that brigatinib exhibits high solubility and high permeability, inhibition of P-gp and BCRP is not expected to result in a clinically meaningful change in the systemic exposure of brigatinib. No dose adjustment is required for Alunbrig during coadministration with P-gp and BCRP inhibitors.

Agents that may decrease brigatinib plasma concentrations

CYP3A inducers

In healthy subjects, coadministration of multiple 600 mg daily doses of rifampicin, a strong CYP3A inducer, with a single 180 mg brigatinib dose decreased brigatinib C_{max} by 60%, AUC_{0-120} by 80% (5-fold), and AUC_{0-120} by 80% (5-fold), relative to a 180 mg brigatinib dose administered alone. The concomitant use of strong CYP3A inducers with Alunbrig, including but not limited to rifampicin, carbamazepine, phenytoin, rifabutin, phenobarbital, and St. John's wort should be avoided.

Moderate CYP3A inducers may decrease the AUC of brigatinib by approximately 50% based on simulations from a physiologically-based pharmacokinetic model. The concomitant use of moderate CYP3A inducers with Alunbrig, including but not limited to efavirenz, modafinil, bosentan, etravirine, and nafcillin should be avoided.

Agents that may have their plasma concentrations altered by brigatinib

CYP3A substrates

In vitro studies in hepatocytes have shown that brigatinib is an inducer of CYP3A4. Clinical drug-drug interaction studies with CYP3A sensitive substrates have not been conducted. Brigatinib may reduce plasma levels of coadministered medicinal products that are predominantly metabolised by CYP3A. Therefore, coadministration of Alunbrig with CYP3A substrates with a narrow therapeutic index (e.g., alfentanil, fentanyl, quinidine, cyclosporine, sirolimus, tacrolimus) should be avoided as their effectiveness may be reduced.

Alunbrig may also induce other enzymes and transporters (e.g., CYP2C, P-gp) via the same mechanisms responsible for induction of CYP3A (e.g., pregnane X receptor activation).

Transporter substrates

Coadministration of brigatinib with substrates of P-gp, (e.g., digoxin, dabigatran, colchicine, pravastatin), BCRP (e.g., methotrexate, rosuvastatin, sulfasalazine), organic cation transporter 1 (OCT1), multidrug and toxin extrusion protein 1 (MATE1), and 2K (MATE2K) may increase their

plasma concentrations. Patients should be closely monitored when Alunbrig is coadministered with substrates of these transporters with a narrow therapeutic index (e.g., digoxin, dabigatran, methotrexate).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing age being treated with Alunbrig should be advised not to become pregnant and men being treated with Alunbrig should be advised not to father a child during treatment. Women of reproductive potential should be advised to use effective non-hormonal contraception during treatment with Alunbrig and for at least 4 months following the final dose. Men with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 3 months after the last dose of Alunbrig.

Pregnancy

Alunbrig may cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity (see section 5.3). There are 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. If Alunbrig is used during pregnancy, or if the patient becomes pregnant while taking this medicinal product, the patient should be apprised of the potential hazard to a foetus.

Breast-feeding

It is unknown whether Alunbrig is excreted in human milk. Available data cannot exclude potential excretion in human milk. Breast-feeding should be stopped during treatment with Alunbrig.

Fertility

No human data on the effect of Alunbrig on fertility are available. Based on repeat-dose toxicity studies in male animals, Alunbrig may cause reduced fertility in males (see section 5.3). The clinical relevance of these findings to human fertility is unknown.

4.7 Effects on ability to drive and use machines

Alunbrig has minor influence on the ability to drive and use machines. However, caution should be exercised when driving or operating machines as patients may experience visual disturbance, dizziness, or fatigue while taking Alunbrig.

4.8 Undesirable effects

Summary of the safety profile

The adverse reactions described in this section were identified from two clinical trials:

Study 201 (ALTA): A randomised, open-label, multicentre trial in patients treated with Alunbrig (N = 219) with ALK+ NSCLC who previously progressed on crizotinib. Patients were randomised in a 1:1 ratio to receive Alunbrig either 90 mg once daily continuously (90 mg regimen) or 180 mg once daily with 7-day lead-in at 90 mg once daily (180 mg regimen).

Study 101: An open-label multicentre phase 1/2 dose escalation/expansion trial in patients with advanced malignancies.

The most common adverse reactions ($\geq 25\%$) reported in patients treated with Alunbrig at the recommended dosing regimen were increased AST, hyperglycaemia, hyperinsulinaemia, anaemia, increased CPK, nausea, increased lipase, decreased lymphocyte count, increased ALT, diarrhoea, increased amylase, fatigue, cough, headache, increased alkaline phosphatase, hypophosphataemia,

increased APTT, rash, vomiting, dyspnoea, hypertension, decreased white blood cell count, myalgia, and peripheral neuropathy.

The most common serious adverse reactions ($\geq 2\%$) reported in patients treated with Alunbrig at the recommended dosing regimen other than events related to neoplasm progression were pneumonitis, pneumonia, and dyspnoea.

Tabulated list of adverse reactions

Adverse reactions reported in ALTA and Study 101 at the recommended dosing regimen are presented in Table 3 and are listed by system organ class, preferred term and frequency. Frequency categories are very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$) and uncommon ($\geq 1/1,000$ to $< 1/100$). Within each frequency grouping, undesirable effects are presented in order of frequency.

Table 3: Adverse reactions reported in patients treated with Alunbrig in ALTA and Study 101 (per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0)

System organ class	Frequency category	Adverse reactions [†] all grades	Adverse reactions Grade 3-4
Infections and infestations	Very common	Pneumonia ^a Upper respiratory tract infection	
	Common		Pneumonia ^a
Blood and lymphatic system disorders	Very common	Anaemia Lymphocyte count decreased APTT increased White blood cell count decreased Neutrophil count decreased Decreased platelet count	Lymphocyte count decreased
	Common		APTT increased Anaemia Neutrophil count decreased
Metabolism and nutrition disorders	Very common	Hyperglycaemia Hyperinsulinaemia ^b Hypophosphataemia Decreased appetite Hypokalaemia Hypomagnesaemia Hyponatraemia Hypercalcaemia	
	Common		Hypophosphataemia Hyperglycaemia Hyponatraemia Hypokalaemia Decreased appetite
Psychiatric disorders	Very common	Insomnia	
Nervous system disorders	Very common	Headache ^c Peripheral neuropathy ^d Dizziness	
	Common	Memory impairment Dysgeusia	Peripheral neuropathy ^d Headache ^c
Eye disorders	Very common	Visual disturbance ^e	
	Common		Visual disturbance ^e

System organ class	Frequency category	Adverse reactions[†] all grades	Adverse reactions Grade 3-4
Cardiac disorders	Common	Tachycardia ^f Electrocardiogram QT prolonged Bradycardia ^g Palpitations	
	Uncommon		Electrocardiogram QT prolonged
Vascular disorders	Very Common	Hypertension	Hypertension
Respiratory, thoracic and mediastinal disorders	Very Common	Cough Dyspnoea ^h	
	Common	Pneumonitis ⁱ	Pneumonitis ⁱ Dyspnoea ^h
Gastrointestinal disorders	Very common	Lipase increased Nausea Diarrhoea ^j Amylase increased Vomiting Constipation Abdominal pain ^k Dry mouth Stomatitis ^l	Lipase increased
	Common	Dyspepsia Flatulence	Amylase increased Abdominal pain ^k
	Uncommon	Pancreatitis	Nausea Dyspepsia Pancreatitis
Hepatobiliary disorders	Very common	AST increased ALT increased Alkaline phosphatase increased	
	Common	Blood lactate dehydrogenase increased Hyperbilirubinaemia	ALT increased AST increased Alkaline phosphatase increased Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Very Common	Rash ^m Pruritus	
	Common	Dry skin Photosensitivity reaction	Rash ^m Photosensitivity reaction
	Uncommon		Dry skin
Musculoskeletal and connective tissue disorders	Very common	Blood CPK increased Myalgia ⁿ Arthralgia Musculoskeletal chest pain	Blood CPK increased
	Common	Pain in extremity Musculoskeletal stiffness	Pain in extremity
	Uncommon		Myalgia ⁿ
Renal and urinary disorders	Very common	Blood creatinine increased	

System organ class	Frequency category	Adverse reactions [†] all grades	Adverse reactions Grade 3-4
General disorders and administration site conditions	Very common	Fatigue ^o Oedema ^p Pyrexia	
	Common	Pain Non-cardiac chest pain Chest discomfort	Fatigue ^o
	Uncommon		Non-cardiac chest pain Pyrexia
Investigations	Common	Weight decreased	
	Uncommon		Weight decreased

^a Includes atypical pneumonia, pneumonia, pneumonia aspiration, pneumonia pseudomonal, lower respiratory tract infection, lower respiratory tract infection viral, lung infection

^b Grade not applicable

^c Includes headache, sinus headache, head discomfort, migraine, tension headache

^d Includes paraesthesia, peripheral sensory neuropathy, dysaesthesia, hyperaesthesia, hypoaesthesia, neuralgia, neuropathy peripheral, neurotoxicity, peripheral motor neuropathy, polyneuropathy

^e Includes altered visual depth perception, asthenopia, cataract, colour blindness acquired, diplopia, glaucoma, intraocular pressure increased, macular oedema, photophobia, photopsia, retinal oedema, vision blurred, visual acuity reduced, visual field defect, visual impairment, vitreous detachment, vitreous floaters, amaurosis fugax

^f Includes sinus tachycardia, tachycardia

^g Includes bradycardia, sinus bradycardia

^h Includes dyspnoea, dyspnoea exertional

ⁱ Includes interstitial lung disease, pneumonitis

^j Includes diarrhoea, diarrhoea infectious

^k Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort

^l Includes aphthous stomatitis, stomatitis, aphthous ulcer, mouth ulceration, oral mucosal blistering

^m Includes dermatitis acneiform, erythema, exfoliative rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, dermatitis, dermatitis allergic, generalised erythema, rash follicular, urticaria

ⁿ Includes musculoskeletal pain, myalgia, muscle spasms, muscle tightness, muscle twitching, musculoskeletal discomfort

^o Includes asthenia, fatigue

^p Includes eyelid oedema, face oedema, localised oedema, oedema peripheral, periorbital oedema, swelling face, generalised oedema, peripheral swelling

[†] The frequencies for ADR terms associated with chemistry and haematology laboratory changes were determined based on the frequency of abnormal laboratory shifts from baseline.

Description of selected adverse reactions

Pulmonary adverse reactions

In ALTA, 6.4% of patients experienced pulmonary adverse reactions of any grade, including ILD/pneumonitis, pneumonia and dyspnoea, early in treatment (within 9 days, median onset: 2 days); 2.7% of patients had Grade 3-4 pulmonary adverse reactions and 1 patient (0.5%) had fatal pneumonia. Following Grade 1-2 pulmonary adverse reactions, treatment with Alunbrig was either interrupted and then restarted or the dose was reduced. Early pulmonary adverse reactions also occurred in a dose escalation study in patients (N = 137) (Study 101) including three fatal cases (hypoxia, acute respiratory distress syndrome and pneumonia).

Additionally, 2.3% of patients in ALTA experienced pneumonitis later in treatment, with 2 patients having Grade 3 pneumonitis (see sections 4.2 and 4.4).

Elderly

In ALTA, 13.5% of patients ≥ 65 years of age experienced an early pulmonary adverse reaction compared with 4.2% of patients < 65 years of age.

Hypertension

In ALTA, hypertension was reported in 28% of patients treated with Alunbrig at the 180 mg regimen with 10% having Grade 3 hypertension. Dose reduction for hypertension occurred in 0.9% at the 180 mg regimen. Mean systolic and diastolic blood pressure, in all patients, increased over time (see sections 4.2 and 4.4).

Bradycardia

In ALTA, bradycardia was reported in 4.5% of patients treated with Alunbrig at the 180 mg regimen.

Heart rates of less than 50 beats per minute (bpm) were reported in 8.2% of patients at the 180 mg regimen. (see sections 4.2 and 4.4).

Visual disturbance

In ALTA, visual disturbance adverse reactions were reported in 18% of patients treated with Alunbrig at the 180 mg regimen. Of these, three Grade 3 adverse reactions (2.7%) including macular oedema and cataract were reported.

Dose reduction for visual disturbance occurred in two patients (1.8%) at the 180 mg regimen (see sections 4.2 and 4.4).

Peripheral neuropathy

In ALTA, peripheral neuropathy adverse reactions were reported in 27.3% of patients treated at the 180 mg regimen. Thirty percent of patients had resolution of all peripheral neuropathy adverse reactions. The median duration of peripheral neuropathy adverse reactions was 4.5 months, with a maximum duration of 28.7 months.

Creatine phosphokinase (CPK) elevation

In ALTA, elevations of CPK were reported in 50% of patients treated with Alunbrig at the 180 mg regimen. The incidence of Grade 3-4 elevations of CPK was 13.6%. The median time to onset for CPK elevations was 27 days.

Dose reduction for CPK elevation occurred in 6.4% patients at the 180 mg regimen (see sections 4.2 and 4.4).

Elevations of pancreatic enzymes

In ALTA, elevations of amylase and lipase were reported in 43% and 50% of patients treated with Alunbrig, respectively at the 180 mg regimen. For elevations to Grade 3 and 4, the incidences for amylase and lipase were 8.2% and 10%, respectively. The median time to onset for amylase elevations and lipase elevations was 17 days and 29 days, respectively.

Dose reduction for elevation of lipase and amylase occurred in 1.8% and 0.9% of patients, respectively at the 180 mg regimen (see sections 4.2 and 4.4).

Elevation of hepatic enzymes

In ALTA, elevations of ALT and AST were reported in 46% and 65% of patients treated with Alunbrig, respectively at the 180 mg regimen. For elevations to Grade 3 and 4, the incidences for ALT and AST were 5.5% and 3.6%, respectively.

No patients had dose reductions due to elevation of ALT or AST.

Hyperglycaemia

In ALTA, 69% of patients experienced hyperglycaemia. Grade 3 hyperglycemia occurred in 7.3% of patients.

No patients had dose reductions due to hyperglycaemia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

There is no specific antidote for overdose with Alunbrig. In the event of an overdose, monitor the patient for adverse reactions (see section 4.8) and provide appropriate supportive care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agent, protein kinase inhibitors, ATC code: L01XE43

Mechanism of action

Brigatinib is a tyrosine kinase inhibitor that targets ALK, c-ros oncogene 1 (ROS1), and insulin-like growth factor 1 receptor (IGF-1R). Brigatinib inhibited autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signalling protein STAT3 in *in vitro* and *in vivo* assays.

Brigatinib inhibited the *in vitro* proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins and demonstrated dose-dependent inhibition of EML4-ALK-positive NSCLC xenograft growth in mice. Brigatinib inhibited the *in vitro* and *in vivo* viability of cells expressing mutant forms of EML4-ALK associated with resistance to ALK inhibitors, including G1202R and L1196M.

Cardiac electrophysiology

In Study 101, the QT interval prolongation potential of Alunbrig was assessed in 123 patients with advanced malignancies following once daily brigatinib doses of 30 mg to 240 mg. The maximum mean QTcF (corrected QT by the Fridericia method) change from baseline was less than 10 msec. An exposure-QT analysis suggested no concentration-dependent QTc interval prolongation.

Clinical efficacy and safety

ALTA

The safety and efficacy of Alunbrig was evaluated in a randomised (1:1), open-label, multicenter trial (ALTA) in 222 adult patients with locally advanced or metastatic ALK-positive NSCLC who had progressed on crizotinib. Eligibility criteria permitted enrolment of patients with a documented ALK rearrangement based on a validated test, ECOG Performance Status of 0-2, and prior chemotherapy. Additionally, patients with central nervous system (CNS) metastases were included, provided they were neurologically stable and did not require an increasing dose of corticosteroids. Patients with a history of pulmonary interstitial disease or drug-related pneumonitis were excluded.

Patients were randomised in a 1:1 ratio to receive Alunbrig either 90 mg once daily (90 mg regimen, N = 112) or 180 mg once daily with 7-day lead-in at 90 mg once daily (180 mg regimen, N = 110). The median duration of follow-up was 22.9 months. Randomisation was stratified by brain metastases (present, absent) and best prior response to crizotinib therapy (complete or partial response, any other response/unknown).

The major outcome measure was confirmed objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumours (RECIST v1.1) as evaluated by investigator. Additional outcome measures included confirmed ORR as evaluated by an Independent Review Committee (IRC); time to response; progression free survival (PFS); duration of response (DOR); overall survival; and intracranial ORR and intracranial DOR as evaluated by an IRC.

Baseline demographics and disease characteristics in ALTA were median age 54 years old (range 18 to 82; 23% 65 and over), 67% White and 31% Asian, 57% female, 36% ECOG PS 0 and 57% ECOG PS 1, 7% ECOG PS2, 60% never smoker, 35% former smoker, 5% current smoker, 98% Stage IV, 97% adenocarcinoma, and 74% prior chemotherapy. The most common sites of

extra-thoracic metastasis included 69% brain (of whom 62% had received prior radiation to the brain), 39% bone, and 26% liver.

Efficacy results from ALTA analysis are summarised in Table 4. and the Kaplan-Meier (KM) curve for investigator-assessed PFS is shown in Figure 1.

Table 4: Efficacy results in ALTA (ITT population)

Efficacy parameter	Investigator assessment		IRC assessment	
	90 mg regimen* N = 112	180 mg regimen† N = 110	90 mg regimen* N = 112	180 mg regimen† N = 110
Objective response rate				
(%)	46%	56%	51%	56%
CI‡	(35, 57)	(45, 67)	(41, 61)	(47, 66)
Time to response				
Median (months)	1.8	1.9	1.8	1.9
Duration of response				
Median (months)	12.0	13.8	16.4	15.7
95% CI	(9.2,17.7)	(10.2,19.3)	(7.4, 24.9)	(12.8, 21.8)
Progression-free survival				
Median (months)	9.2	15.6	9.2	16.7
95% CI	(7.4, 11.1)	(11.1, 21)	(7.4, 12.8)	(11.6, 21.4)
Overall survival				
Median (months)	29.5	34.1	NA	NA
95% CI	(18.2, NE)	(27.7, NE)	NA	NA
12-month survival probability (%)	70.3%	80.1%	NA	NA

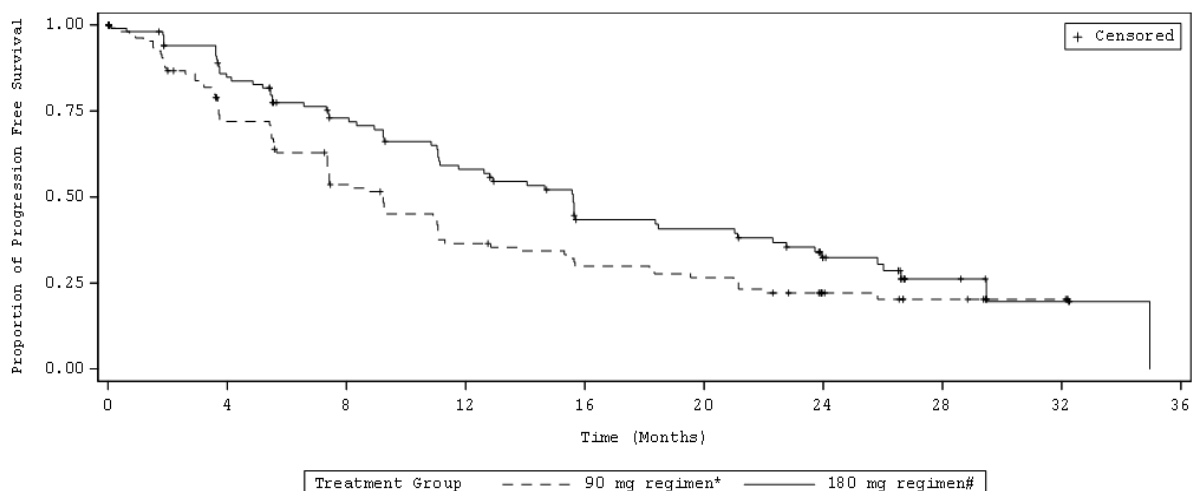
CI = Confidence Interval; NE = Not Estimable; NA = Not Applicable

*90 mg once daily regimen

†180 mg once daily with 7-day lead-in at 90 mg once daily

‡Confidence Interval for investigator assessed ORR is 97.5% and for IRC assessed ORR is 95%

Figure 1: Investigator-Assessed Systemic Progression-Free Survival: ITT Population by Treatment Arm (ALTA)



Abbreviations: ITT = Intent-to-treat

Note: Progression-Free survival was defined as time from initiation of treatment until the date at which disease progression was first evident or death, whichever comes first.

*90 mg once daily regimen

†180 mg once daily with 7-day lead-in at 90 mg once daily

IRC assessments of intracranial ORR and duration of intracranial response in patients from ALTA with measurable brain metastases (≥ 10 mm in longest diameter) at baseline are summarised in Table 5.

Table 5: Intracranial efficacy in patients with measurable brain metastases at baseline in ALTA

IRC-assessed efficacy parameter	Patients with measurable brain metastases at baseline	
	90 mg regimen* (N = 26)	180 mg regimen† (N = 18)
Intracranial objective response rate		
(%)	50%	67%
95% CI	(30, 70)	(41, 87)
Intracranial disease control rate		
(%)	85%	83%
95% CI	(65, 96)	(59, 96)
Duration of intracranial response‡,		
Median (months)	9.4	16.6
95% CI	(3.7, 24.9)	(3.7, NE)

% CI = Confidence Interval; NE = Not Estimable

*90 mg once daily regimen

†180 mg once daily with 7-day lead-in at 90 mg once daily

‡Events include intracranial disease progression (new lesions, intracranial target lesion diameter growth $\geq 20\%$ from nadir, or unequivocal progression of intracranial non-target lesions) or death.

In patients with any brain metastases at baseline, intracranial disease control rate was 77.8% (95% CI 67.2-86.3) in the 90 mg arm (N = 81) and 85.1% (95% CI 75-92.3) in the 180 mg arm (N=74).

Study 101

In a separate dose finding study, 25 patients with ALK-positive NSCLC that progressed on crizotinib were administered Alunbrig at 180 mg once daily with 7-day lead-in at 90 mg once daily regimen. Of these, 19 patients had an investigator-assessed confirmed objective response (76%; 95% CI: 55, 91) and the KM estimate median duration of response among the 19 responders was 26.1 months (95% CI: 7.9, 26.1). The KM median PFS was 16.3 months (95% CI: 9.2, NE) and the 12-month probability of overall survival was 84.0% (95% CI: 62.8, 93.7).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Alunbrig in all subsets of the paediatric population in lung carcinoma (small cell and non-small cell carcinoma) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

In Study 101, following administration of a single oral dose of brigatinib (30-240 mg) in patients, the median time to peak concentration (T_{max}) was 1-4 hours postdose. After a single dose and at steady state, systemic exposure was dose proportional over the dose range of 60-240 mg once daily. Modest accumulation was observed upon repeated dosing (geometric mean accumulation ratio: 1.9 to 2.4). The geometric mean steady state C_{max} of brigatinib at doses of 90 mg and 180 mg once daily was 552 and 1,452 ng/mL, respectively, and the corresponding $AUC_{0-\tau}$ was 8,165 and 20,276 h·ng/mL, respectively. Brigatinib is a substrate of the transporter proteins P-gp and BCRP.

In healthy subjects, compared to overnight fasting, a high fat meal reduced brigatinib C_{max} by 13% with no effect on AUC. Brigatinib can be administered with or without food.

Distribution

Brigatinib was moderately bound (91%) to human plasma proteins and binding was not concentration-dependent. The blood-to-plasma concentration ratio is 0.69. In patients given brigatinib 180 mg once daily, the geometric mean apparent volume of distribution (V_zF) of brigatinib at steady state was 153 L, indicating moderate distribution into tissues.

Biotransformation

In vitro studies demonstrated that brigatinib is primarily metabolised by CYP2C8 and CYP3A4, and to a much lesser extent by CYP3A5.

Following oral administration of a single 180 mg dose of [^{14}C]brigatinib to healthy subjects, N-demethylation and cysteine conjugation were the two major metabolic clearance pathways. In urine and faeces combined, 48%, 27%, and 9.1% of the radioactive dose was excreted as unchanged brigatinib, N-desmethyl brigatinib (AP26123), and brigatinib cysteine conjugate, respectively. Unchanged brigatinib was the major circulating radioactive component (92%) along with AP26123 (3.5%), the primary metabolite also observed *in vitro*. In patients, at steady state, the plasma AUC of AP26123 was < 10% of brigatinib exposure. In *in vitro* kinase and cellular assays, the metabolite, AP26123, inhibited ALK with approximately 3-fold lower potency than brigatinib.

Elimination

In patients given brigatinib 180 mg once daily, the geometric mean apparent oral clearance (CL/F) of brigatinib at steady state was 13 L/h and the median plasma elimination half-life was 24 h.

The primary route of excretion of brigatinib is in faeces. In six healthy male subjects given a single 180 mg oral dose of [^{14}C]brigatinib, 65% of the administered dose was recovered in faeces and 25% of the administered dose was recovered in urine. Unchanged brigatinib represented 41% and 86% of the total radioactivity in faeces and urine, respectively, the remainder being metabolites.

Specific populations

Hepatic impairment

The pharmacokinetics of brigatinib was characterised in healthy subjects with normal hepatic function (N = 9), and patients with mild hepatic impairment (Child-Pugh class A, N = 6), moderate hepatic impairment (Child-Pugh class B, N = 6), or severe hepatic impairment (Child-Pugh class C, N = 6). The pharmacokinetics of brigatinib was similar between healthy subjects with normal hepatic function and patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. Unbound AUC_{0-INF} was 37% higher in patients with severe hepatic impairment (Child-Pugh class C) as compared to healthy subjects with normal hepatic function (see section 4.2).

Renal impairment

The pharmacokinetics of brigatinib is similar in patients with normal renal function and in patients with mild or moderate renal impairment (eGFR \geq 30 mL/min) based on the results of population pharmacokinetic analyses. In a pharmacokinetic study, unbound AUC_{0-INF} was 94% higher in patients with severe renal impairment (eGFR < 30 mL/min, N = 6) as compared to patients with normal renal function (eGFR \geq 90 mL/min, N = 8) (see section 4.2).

Race and gender

Population pharmacokinetic analyses showed that race and gender had no impact on the pharmacokinetics of brigatinib.

Age, body weight, and albumin concentrations

The population pharmacokinetic analyses showed that body weight, age, and albumin concentration had no clinically relevant impact on the pharmacokinetics of brigatinib.

5.3 Preclinical safety data

Safety pharmacology studies with brigatinib identified potential for pulmonary effects (altered respiration rate; 1-2 times the human C_{max}), cardiovascular effects (altered heart rate and blood pressure; at 0.5 times the human C_{max}), and renal effects (reduced renal function; at 1-2.5 times the human C_{max}), but did not indicate any potential for QT prolongation or neurofunctional effects.

Adverse reactions seen in animals at exposure levels similar to clinical exposure levels with possible relevance to clinical use were as follows: gastrointestinal system, bone marrow, eyes, testes, liver, kidney, bone, and heart. These effects were generally reversible during the non-dosing recovery period; however, effects in the eyes and testes were notable exceptions due to lack of recovery. In repeated dose toxicity studies, lung changes (foamy alveolar macrophages) were noted in monkeys at ≥ 0.2 times the human AUC; however, these were minimal and similar to those reported as background findings in naive monkeys, and there was no clinical evidence of respiratory distress in these monkeys.

Carcinogenicity studies have not been performed with brigatinib.

Brigatinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) or the mammalian cell chromosomal aberration assays, but slightly increased the number of micronuclei in a rat bone marrow micronucleus test. The mechanism of micronucleus induction was abnormal chromosome segregation (aneugenicity) and not a clastogenic effect on chromosomes. This effect was observed at approximately five fold the human exposure at the 180 mg once daily dose.

Brigatinib may impair male fertility. Testicular toxicity was observed in repeat-dose animal studies. In rats, findings included lower weight of testes, seminal vesicles and prostate gland, and testicular tubular degeneration; these effects were not reversible during the recovery period. In monkeys, findings included reduced size of testes along with microscopic evidence of hypospermatogenesis; these effects were reversible during the recovery period. Overall, these effects on the male reproductive organs in rats and monkeys occurred at exposures ≥ 0.2 -times the AUC observed in patients at the 180 mg once daily dose. No apparent adverse effects on female reproductive organs were observed in general toxicology studies in rats and monkeys.

In an embryo-foetal development study in which pregnant rats were administered daily doses of brigatinib during organogenesis; dose-related skeletal anomalies were observed at doses as low as approximately 0.7-times the human exposure by AUC at the 180 mg once daily dose. Findings included embryo-lethality, reduced foetal growth, and skeletal variations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate (type A)
Silica colloidal hydrophobic
Magnesium stearate

Tablet coating

Talc
Macrogol
Polyvinyl alcohol
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Alunbrig 30 mg film-coated tablets

3 years

Alunbrig 90 mg film-coated tablets

2 years

Alunbrig 180 mg film-coated tablets

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alunbrig 30 mg film-coated tablets

Round wide mouth high density polyethylene (HDPE) bottles with two-piece polypropylene child resistant screw cap closures with foil induction seal liner, containing either 60 or 120 film-coated tablets, together with one HDPE canister containing a molecular sieve desiccant.

Clear thermoformable poly-chloro-tri-fluoro-ethylene (PCTFE) blister with heat sealable paper-laminated foil lidding in a carton, containing either 28, 56 or 112 film-coated tablets.

Alunbrig 90 mg film-coated tablets

Round wide mouth high density polyethylene (HDPE) bottles with two-piece polypropylene child resistant screw cap with foil induction seal liner closures, containing either 7 or 30 film-coated tablets, together with one HDPE canister containing a molecular sieve desiccant.

Clear thermoformable poly-chloro-tri-fluoro-ethylene (PCTFE) blister with heat sealable paper-laminated foil lidding in a carton, containing either 7 or 28 film-coated tablets.

Alunbrig 180 mg film-coated tablets

Round wide mouth high density polyethylene (HDPE) bottles with two-piece polypropylene child resistant screw cap with foil induction seal liner closures, containing 30 film-coated tablets, together with one HDPE canister containing a molecular sieve desiccant.

Clear thermoformable poly-chloro-tri-fluoro-ethylene (PCTFE) blister with heat sealable paper-laminated foil lidding in a carton, containing 28 film-coated tablets.

Treatment initiation pack Alunbrig 90 mg and 180 mg film-coated tablets

Each pack consists of an outer carton with two inner cartons containing:

- Alunbrig 90 mg film-coated tablets
1 clear thermoformable poly-chloro-tri-fluoro-ethylene (PCTFE) blister with heat sealable paper-laminated foil lidding in a carton, containing 7 film-coated tablets.
- Alunbrig 180 mg film-coated tablets
3 clear thermoformable poly-chloro-tri-fluoro-ethylene (PCTFE) blisters with heat sealable paper-laminated foil lidding in a carton, containing 21 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Patients should be advised to keep the desiccant canister in the bottle and not to swallow it.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

Alunbrig 30 mg film-coated tablets

EU/1/18/1264/001	60 tablets in bottle
EU/1/18/1264/002	120 tablets in bottle
EU/1/18/1264/011	28 tablets in carton
EU/1/18/1264/003	56 tablets in carton
EU/1/18/1264/004	112 tablets in carton

Alunbrig 90 mg film-coated tablets

EU/1/18/1264/005	7 tablets in bottle
EU/1/18/1264/006	30 tablets in bottle
EU/1/18/1264/007	7 tablets in carton
EU/1/18/1264/008	28 tablets in carton

Alunbrig 180 mg film-coated tablets

EU/1/18/1264/009	30 tablets in bottle
EU/1/18/1264/010	28 tablets in carton

Alunbrig treatment initiation pack

EU/1/18/1264/012	7 x 90 mg + 21 x 180 mg tablets in carton
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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Takeda Austria GmbH
St. Peter-Strasse 25
4020 Linz
Austria

Penn Pharmaceutical Services Limited
Units 23-24
Tafarnaubach Industrial Estate
Gwent
Tredegar
NP22 3AA
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Alunbrig in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Alunbrig is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Alunbrig have access to/are provided with the following educational package:

A patient alert card

- **The patient alert card** shall contain the following key messages:
 - A warning message for health care professionals treating the patient at any time, including in conditions of emergency, that the patient is using Alunbrig
 - That Alunbrig treatment may increase the risk of early onset pulmonary events (including interstitial lung disease and pneumonitis)
 - Signs or symptoms of the safety concern and when to seek attention from a HCP
 - Contact details of the Alunbrig prescriber

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further characterise the efficacy and safety of brigatinib in the treatment of patients with ALK positive NSCLC, the MAH should submit the clinical study report of the phase III study AP26113-13-301 comparing brigatinib versus crizotinib in patients with advanced ALK+ NSCLC who have not previously received ALK-directed therapy.	31 Dec 2020

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Alunbrig 30 mg film-coated tablets
brigatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 30 mg brigatinib.

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
60 film-coated tablets
120 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Outer carton:
Do not swallow the desiccant canister found in the bottle.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1264/001 60 tablets
EU/1/18/1264/002 120 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer Carton:
Alunbrig 30 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Outer Carton:
PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Alunbrig 30 mg film-coated tablets
brigatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 30 mg brigatinib.

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
28 film-coated tablets
56 film-coated tablets
112 film coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1264/011 28 tablets
EU/1/18/1264/003 56 tablets
EU/1/18/1264/004 112 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Alunbrig 30 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Alunbrig 30 mg film-coated tablets
brigatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Alunbrig 90 mg film-coated tablets
brigatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 90 mg brigatinib.

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
7 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Outer carton:
Do not swallow the desiccant canister found in the bottle.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1264/005 7 tablets
EU/1/18/1264/006 30 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer Carton:
Alunbrig 90 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Outer Carton
PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Alunbrig 90 mg film-coated tablets
brigatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 90 mg brigatinib.

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
7 film-coated tablets
28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1264/007 7 tablets
EU/1/18/1264/008 28 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Alunbrig 90 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Alunbrig 90 mg film-coated tablets
brigatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR TREATMENT INITIATION PACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Alunbrig 90 mg film-coated tablets
Alunbrig 180 mg film-coated tablets
brigatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 90 mg film-coated tablet contains 90 mg brigatinib.
Each 180 mg film-coated tablet contains 180 mg brigatinib.

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Treatment initiation pack
Each pack contains two cartons in an outer carton.
7 film-coated tablets of Alunbrig 90 mg
21 film-coated tablets of Alunbrig 180 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

Take only one tablet per day.

Alunbrig 90 mg once daily for the first 7 days, then Alunbrig 180 mg once daily.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1264/012 7 x 90 mg + 21 x 180 mg tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Alunbrig 90 mg, 180 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON FOR TREATMENT INITIATION PACK – 7 TABLETS, 90 MG – 7 DAY TREATMENT (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Alunbrig 90 mg film-coated tablets
brigatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 90 mg brigatinib.

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
Treatment initiation pack
Each pack contains 7 film-coated tablets of Alunbrig 90 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

Take only one tablet per day.

Alunbrig 90 mg
brigatinib
Day 1 to Day 7
7 tablets of Alunbrig 90 mg

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1264/012 7 x 90 mg + 21 x 180 mg tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Alunbrig 90 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER – TREATMENT INITIATION PACK – 90 MG

1. NAME OF THE MEDICINAL PRODUCT

Alunbrig 90 mg film-coated tablets
brigatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**INNER CARTON FOR TREATMENT INITIATION PACK – 21 TABLETS, 180 MG –
21 DAY TREATMENT (WITHOUT BLUE BOX)**

1. NAME OF THE MEDICINAL PRODUCT

Alunbrig 180 mg film-coated tablets
brigatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 180 mg brigatinib.

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
Treatment initiation pack
Each pack contains 21 film-coated tablets of Alunbrig 180 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

Take only one tablet per day.

Alunbrig 180 mg
brigatinib
Day 8 to Day 28
21 tablets of Alunbrig 180 mg

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1264/012 7 x 90 mg + 21 x 180 mg tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Alunbrig 180 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER – TREATMENT INITIATION PACK – 180 MG

1. NAME OF THE MEDICINAL PRODUCT

Alunbrig 180 mg film-coated tablets
brigatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Alunbrig 180 mg film-coated tablets
brigatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 180 mg brigatinib.

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Outer carton:
Do not swallow the desiccant canister found in the bottle.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1264/009 30 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer Carton:
Alunbrig 180 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Outer Carton
PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Alunbrig 180 mg film-coated tablets
brigatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 180 mg brigatinib.

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1264/010 28 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Alunbrig 180 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Alunbrig 180 mg film-coated tablets
brigatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Alunbrig 30 mg film-coated tablets
Alunbrig 90 mg film-coated tablets
Alunbrig 180 mg film-coated tablets
brigatinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Alunbrig is and what it is used for
2. What you need to know before you take Alunbrig
3. How to take Alunbrig
4. Possible side effects
5. How to store Alunbrig
6. Contents of the pack and other information

1. What Alunbrig is and what it is used for

Alunbrig contains the active substance brigatinib, a type of cancer medicine called a kinase inhibitor. Alunbrig is used to treat adults with advanced stages of a **lung cancer** called non-small cell lung cancer. It is given to patients whose lung cancer is related to an abnormal form of a gene called anaplastic lymphoma kinase (*ALK*).

How Alunbrig works

The abnormal gene produces a protein known as a kinase that stimulates the growth of the cancer cells. Alunbrig blocks the action of this protein and thus slows down the growth and spread of the cancer.

2. What you need to know before you take Alunbrig

Do not take Alunbrig:

- if you are **allergic** to brigatinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor before taking Alunbrig or during treatment if you have:

- **lung or breathing problems**
Lung problems, some severe, are more frequent within the first 7 days of treatment. Symptoms may be similar to symptoms from lung cancer. Tell your doctor of any new or worsening symptoms including breathing discomfort, shortness of breath, chest pain, cough and fever.
- **high blood pressure**
- **a slow heartbeat (bradycardia)**
- **vision disturbance**
Inform your doctor of any visual disturbance that occurs during treatment, such as seeing flashes of light, blurry vision or light hurting your eyes.
- **muscle problems**
Report any unexplained muscle pain, tenderness or weakness to your doctor.
- **pancreas problems**
- **liver problems**
- **high blood sugar**

Tell your doctor if you have kidney problems or you are on dialysis.

Your doctor may need to adjust your treatment or stop Alunbrig temporarily or permanently. See also the beginning of section 4.

Children and adolescents

Alunbrig has not been studied in children or adolescents. Treatment with Alunbrig is not recommended in persons under 18 years of age.

Other medicines and Alunbrig

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

The following medicines can affect or be affected by Alunbrig:

- **ketoconazole, itraconazole, voriconazole:** medicines to treat fungal infections
- **indinavir, nelfinavir, ritonavir, saquinavir:** medicines to treat HIV infection
- **clarithromycin, telithromycin, troleandomycin:** medicines to treat bacterial infections
- **mibefradil:** a medicine to treat irregular heart rhythm and high blood pressure
- **nefazodone:** a medicine to treat depression
- **St. John's wort:** a herbal product used to treat depression
- **carbamazepine:** a medicine to treat epilepsy, euphoric/depressive episodes and certain pain conditions
- **phenobarbital, phenytoin:** medicines to treat epilepsy
- **rifabutin, rifampicin:** medicines to treat tuberculosis or certain other infections
- **digoxin:** a medicine to treat heart problems
- **dabigatran:** a medicine to inhibit blood clotting
- **colchicine:** a medicine to treat gout attacks
- **pravastatin, rosuvastatin:** medicines to lower elevated cholesterol levels
- **methotrexate:** a medicine to treat severe joint inflammation, cancer and the skin disease psoriasis
- **sulfasalazine:** a medicine to treat severe bowel and rheumatic joint inflammation
- **efavirenz, etravirine:** medicines to treat HIV infection
- **modafinil:** a medicine to treat narcolepsy
- **bosentan:** a medicine to treat pulmonary hypertension

- **nafcillin:** a medicine to treat bacterial infections
- **alfentanil, fentanyl:** medicines to treat pain
- **quinidine:** a medicine to treat irregular heart rhythm
- **cyclosporine, sirolimus, tacrolimus:** medicines to suppress the immune system

Alunbrig with food and drink

Avoid any grapefruit products during treatment as they may change the amount of brigatinib in your body.

Pregnancy

Alunbrig is **not recommended** during pregnancy unless the benefit outweighs the risk to the baby. If you are pregnant or think you may be pregnant or are planning to have a baby, talk to your doctor to discuss the risks of taking Alunbrig during pregnancy.

Women of childbearing age being treated with Alunbrig should avoid becoming pregnant. Effective non-hormonal contraception must be used during treatment and for 4 months after stopping Alunbrig. Ask your doctor about the birth control methods that may be right for you.

Breast-feeding

Do not breast-feed during treatment with Alunbrig. It is unknown if brigatinib passes into breast milk and could potentially harm the baby.

Fertility

Men receiving treatment with Alunbrig are advised not to father a child during treatment and to use effective contraception during treatment and for 3 months after stopping.

Driving and using machines

Alunbrig may cause visual disturbances, dizziness or tiredness. Do not drive or use machines during treatment if such signs occur.

Alunbrig contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Alunbrig

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is

One 90 mg tablet once daily for the first 7 treatment days; thereafter, one 180 mg tablet once daily. Do not change the dose without talking to your doctor. Your doctor may adjust your dose according to your needs and this may require use of a 30 mg tablet to achieve the new recommended dose.

Treatment initiation pack

At the beginning of your treatment with Alunbrig your doctor may prescribe a treatment initiation pack.

Method of use

- Take Alunbrig once daily at the same time each day.
- Swallow the tablets whole, with a glass of water. Do not crush or dissolve the tablets.
- The tablets can be taken with or without food.
- If you vomit after taking Alunbrig, do not take any more tablets until your next scheduled dose.

Do not swallow the desiccant canister contained in the bottle.

If you take more Alunbrig than you should

Tell your doctor or pharmacist right away if you have taken more tablets than recommended.

If you forget to take Alunbrig

Do not take a double dose to make up for a forgotten dose. Take your next dose at your regular time.

If you stop taking Alunbrig

Do not stop taking Alunbrig before talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or pharmacist immediately if you have any of the following serious side effects:

Very common (may affect more than 1 in 10 people):

- **high blood pressure**
Tell your doctor if you get headaches, dizziness, blurred vision, chest pain or shortness of breath.
- **vision problems**
Tell your doctor if you experience any visual disturbances, such as seeing flashes of light, blurry vision or light hurting eyes. Your doctor may stop Alunbrig treatment and refer you to an ophthalmologist.
- **increased blood level of creatine phosphokinase in tests** – may indicate muscle damage, such as of the heart. Tell your doctor if you have any unexplained muscle pain, tenderness or weakness.
- **increased blood levels of amylase or lipase in tests** – may indicate inflammation of the pancreas
Tell your doctor if you have upper abdominal pain, including abdominal pain that gets worse with eating and may spread to the back, weight loss or nausea.
- **increased blood levels of liver enzymes (aspartate aminotransferase, alanine aminotransferase) in tests** -may indicate liver cell damage. Tell your doctor if you have pain on the right side of your stomach area, yellowing of your skin or the whites of your eyes, or dark urine.
- **increased blood sugar**
Tell your doctor if you are feeling very thirsty, need to urinate more than usual, feeling very hungry, sick to your stomach, weak or tired, or confused.

Common (may affect up to 1 in 10 people):

- **lung inflammation**
Tell your doctor if you have any new or worsening lung or breathing problems, including chest pain, cough, and fever, especially within the first week of taking Alunbrig, as they may be a sign of serious lung problems.
- **slow heartbeat**
Tell your doctor if you have chest pain or discomfort, changes in heartbeat, dizziness, light-headedness or fainting.
See also section 2, “Warnings and precautions”.

Other possible side effects are:

Tell your doctor or pharmacist if you notice any of the following side effects

Very common (may affect more than 1 in 10 people):

- lung infection (pneumonia)
- cold-like symptoms (upper respiratory tract infection)
- reduced number of red blood cells (anaemia)
- reduced number of white blood cells, called neutrophils and lymphocytes, in blood tests
- increased blood clotting time shown by test of activated partial thromboplastin time
- low platelet counts in blood tests, which may increase the risk of bleeding and bruising
- increased blood level of insulin
- reduced blood level of phosphorus
- decreased appetite
- reduced blood level of potassium
- reduced blood level of magnesium
- reduced blood level of sodium
- increased blood level of calcium
- difficulty sleeping (insomnia)
- headache
- symptoms such as numbness, tingling, prickling sensation, weakness or pain in hands or feet (peripheral neuropathy)
- dizziness
- cough
- shortness of breath
- nausea
- diarrhoea
- vomiting
- constipation
- abdominal (belly) pain
- dry mouth
- inflammation of the mouth and lips (stomatitis)
- increased blood level of the enzyme alkaline phosphatase – may indicate organ malfunction or injury
- rash
- skin itching
- joint or muscle pain
- musculoskeletal chest pain
- increased blood level of creatinine – may indicate reduced kidney function
- fatigue
- tissue swelling caused by excess fluid
- fever

Common (may affect up to 1 in 10 people):

- memory impairment
- change in sense of taste

- rapid heartbeat (tachycardia)
- abnormal electrical activity of the heart (prolonged electrocardiogram QT interval)
- palpitations
- indigestion
- flatulence
- increased blood level of lactate dehydrogenase – may indicate tissue breakdown
- increased blood level of bilirubin
- dry skin
- sensitivity to sunlight
- pain in arms and legs
- muscle and joint stiffness
- pain
- chest pain and discomfort
- weight loss

Uncommon (may affect up to 1 in 100 people)

- inflammation of pancreas which may cause severe and persistent stomach pain, with or without nausea and vomiting (pancreatitis)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the [national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Alunbrig

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on either the bottle label or blister and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via waste water or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Alunbrig contains

- The active substance is brigatinib.
Each 30 mg film-coated tablet contains 30 mg brigatinib.
Each 90 mg film-coated tablet contains 90 mg brigatinib.
Each 180 mg film-coated tablet contains 180 mg brigatinib.
- The other excipients are lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (type A), silica colloidal hydrophobic, magnesium stearate, talc, macrogol, polyvinyl alcohol, and titanium dioxide.

What Alunbrig looks like and contents of the pack

Alunbrig film-coated tablets are white to off-white, oval (90 mg and 180 mg) or round (30 mg). They are convex on the upper and lower side.

Alunbrig 30 mg:

- Each 30 mg tablet contains 30 mg brigatinib.
- The film-coated tablets are approximately 7 mm in diameter with “U3” on one side and plain on the other side.

Alunbrig 90 mg:

- Each 90 mg tablet contains 90 mg brigatinib.
- The film-coated tablets are approximately 15 mm long with “U7” on one side and plain on the other side.

Alunbrig 180 mg:

- Each 180 mg tablet contains 180 mg brigatinib.
- The film-coated tablets are approximately 19 mm long with “U13” on one side and plain on the other side.

Alunbrig is available in plastic foil strips (blisters) packed in a carton with:

- Alunbrig 30 mg: 28, 56 or 112 film-coated tablets
- Alunbrig 90 mg: 7 or 28 film-coated tablets
- Alunbrig 180 mg: 28 film-coated tablets

Alunbrig is available in plastic bottles with child resistant screw top closures. Each bottle contains one canister of a desiccant and is packed in a carton with:

- Alunbrig 30 mg: 60 or 120 film-coated tablets
- Alunbrig 90 mg: 7 or 30 film-coated tablets
- Alunbrig 180 mg: 30 film-coated tablets

Alunbrig is available as a treatment initiation pack. Each pack consists of an outer carton with two inner cartons containing:

- Alunbrig 90 mg film-coated tablets
1 plastic foil strip (blister), containing 7 film-coated tablets
- Alunbrig 180 mg film-coated tablets
3 plastic foil strips (blisters), containing 21 film-coated tablets

Keep the desiccant canister in the bottle.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Takeda Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

Manufacturer

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St. Peter-Strasse 25
4020 Linz
Austria

Penn Pharmaceutical Services Limited
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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>.