SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Briganix 180mg Tablet

2. Qualitative and quantitative composition

Briganix 180mg Tablet

Each tablet contains 180mg of Brigatinib.

3. Pharmaceutical form Tablet.

Brigatinib 180mg Tablet

A light yellowish diamond shaped film coated tablet break line on one side and plain in other side.

4. Clinical particulars

4.1 Therapeutic indications

Brigatinib 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 Brigatinib 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 Brigatinib therapy. A validated ALK assay is necessary for the selection of ALK-positive NSCLC patients. 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 Brigatinib is 90 mg once daily for the first 7 days, then 180 mg once daily.

If Brigatinib 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.

Brigatinib dose modification levels are summarized in Table 1.

Table 1: Recommended Brigatinib 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

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

Recommendations for dose modifications of Brigatinib for the management of adverse reactions are summarized in Table 2.

Table 2: Recommended Brigatinib dose modifications for adverse reactions

Adverse reaction	**Severity***	**Dose modification**

Interstitial lung disease (ILD)/pneumonitis	Grade 1	• If event occurs during the first 7 days of treatment, Brigatinib 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, Brigatinib should be withheld until recovery to baseline, then resumed at same dose level. • If ILD/pneumonitis recurs, Brigatinib should be permanently discontinued.
	Grade 2	• If ILD/pneumonitis occurs during the first 7 days of treatment, Brigatinib 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, Brigatinib should be withheld until recovery to baseline. Brigatinib should be resumed at next lower dose level as described in Table 1. • If ILD/pneumonitis recurs, Brigatinib should be permanently discontinued.
	Grade 3 or 4	• Brigatinib should be permanently discontinued.
Hypertension	Grade 3 hypertension (SBP ≥ 160 mmHg or DBP ≥ 100 mmHg, medical intervention indicated, more than one anti-hypertensive medicinal product, or more intensive therapy than previously used indicated)	• Brigatinib should be withheld until hypertension has recovered to Grade ≤ 1 (SBP < 140 mmHg and DBP < 90 mmHg), then resumed at same dose. • If Grade 3 hypertension recurs, Brigatinib should be withheld until hypertension has recovered to Grade ≤ 1 then resumed at the next lower dose level per Table 1 or permanently discontinued
	Grade 4 hypertension (life threatening consequences, urgent intervention indicated)	• 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 per Table 1 or permanently discontinued. • If Grade 4 hypertension recurs, Brigatinib should be permanently discontinued.
Bradycardia (HR less than 60 bpm)	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 per Table 1 upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above.

	Bradycardia with lifethreatening consequences, urgent intervention indicated	• If contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, Brigatinib 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. • 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 elevation of CPK (> 5.0 × ULN)	• Brigatinib should be withheld until recovery to Grade ≤ 1 (≤ 2.5 × ULN) or to baseline, then resumed at the same dose. • If Grade 3 elevation of CPK recurs, Brigatinib should be withheld until recovery to Grade ≤ 1 (≤ 2.5 × ULN) or to baseline, then resumed at the next lower dose level per Table 1.
	Grade 4 elevation of CPK (> 10.0 × ULN)	• Brigatinib should be withheld until recovery to Grade ≤ 1 (≤ 2.5 × 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 × ULN)	• 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 per Table 1.
	Grade 4 elevation of 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 per Table 1.
Hepatotoxicity	Grade ≥ 3 elevation (> 5.0 × ULN) of either alanine aminotransferase (ALT) or aspartate	• Brigatinib should be withheld until recovery to baseline or less than or equal to 3 × ULN, then resumed at next lower dose per Table 1.
	aminotransferase (AST) with bilirubin ≤ 2 × ULN	
	Grade ≥ 2 elevation (> 3 × ULN) of ALT or AST with concurrent total bilirubin elevation > 2 × ULN in the absence of cholestasis or haemolysis	• Brigatinib should be permanently discontinued.
Hyperglycaemia	For Grade 3 (greater than 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 per Table 1 or permanently discontinued.
Visual Disturbance	Grade 2 or 3	• Brigatinib should be withheld until recovery to Grade 1 or baseline, then resumed at the next lower dose level per Table 1.
	Grade 4	• Brigatinib should be permanently discontinued.

Other adverse reactions	Grade 3	• Brigatinib should be withheld until recovery to baseline, then resumed at the same dose level. • If the Grade 3 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.
	Grade 4	• 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.
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 Brigatinib in patients aged 65 years and older suggest that a dose adjustment is not required in elderly patients. There are no available data on patients over 85 years of age.

Hepatic impairment

No dose adjustment of Brigatinib 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 (ChildPugh class C).

Renal impairment

No dose adjustment of Brigatinib is required for patients with mild or moderate renal impairment (estimated glomerular filtration rate (eGFR) ≥ 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). 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.

Peddiatric population

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

Method of administration

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

Grapefruit or grapefruit juice may increase plasma concentrations of brigatinib and should be avoided.

4.3 Contraindications

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

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 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 trial.

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. Evidence of pneumonitis in any patient with worsening respiratory symptoms should be promptly investigated. If pneumonitis is suspected, the dose of Brigatinib should be withheld, and the patient evaluated for other causes of symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). The dose should be modified accordingly. **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. For severe hypertension (≥ Grade 3), Brigatinib should be withheld until hypertension has recovered to Grade 1 or to baseline. The dose should be modified accordingly.

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 symptomatic bradycardia occurs, treatment with Brigatinib should be withheld and concomitant medicinal products known to cause bradycardia should be evaluated. Upon recovery, the dose should be modified accordingly. In case of life-threatening bradycardia, if no contributing concomitant medication is identified or in case of recurrence, treatment with Brigatinib should be discontinued.

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.

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. Based on the severity of the CPK elevation, treatment with Brigatinib should be withheld, and the dose modified accordingly.

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 . Based on the severity of the laboratory abnormalities, treatment with Brigatinib should be withheld, and the dose modified accordingly.

Hepatotoxicity

Elevations of hepatic enzymes (aspartate aminotransferase, alanine aminotransferase) 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. Based on the severity of the laboratory abnormalities, treatment should be withheld, and the dose modified accordingly.

Hyperglycemia

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 1 may be considered or Brigatinib may be permanently discontinued.

Drug-drug interactions

The concomitant use of Brigatinib with strong CYP3A inhibitors should be avoided. If concomitant use of strong CYP3A inhibitors cannot be avoided, the dose of Brigatinib should be reduced from 180 mg to 90 mg, or from 90 mg to 60 mg. 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.

The concomitant use of Brigatinib with strong and moderate CYP3A inducers should be avoided.

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.

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 Cmax by 21%, AUC $_{0\text{-INF}}$ 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 Brigatinib , 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 Brigatinib 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, Brigatinib 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 Brigatinib in combination with moderate CYP3A inhibitors. Patients should be closely monitored when Brigatinib is coadministered with moderate CYP3A inhibitors.

Grapefruit or grapefruit juice may also increase plasma concentrations of brigatinib and should be avoided. 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 Cmax by 41%, AUC0-INF by 12%, and AUC0-120 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 Brigatinib 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 Cmax by 60%, AUC0-INF by 80% (5fold), and AUC0-120 by 80% (5-fold), relative to a 180 mg brigatinib dose administered alone. The concomitant use of strong CYP3A inducers with Brigatinib , 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 Brigatinib , 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 Brigatinib 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.

Brigatinib 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 Brigatinib 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 Brigatinib should be advised not to become pregnant and men being treated with Brigatinib 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 Brigatinib 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 Brigatinib .

Pregnancy

Brigatinib may cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity. There are no clinical data on the use of Brigatinib in pregnant women. Brigatinib should not be used during pregnancy unless the clinical condition of the mother requires treatment. If Brigatinib 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 Brigatinib is excreted in human milk. Available data cannot exclude potential excretion in human milk. Breast-feeding should be stopped during treatment with Brigatinib .

Fertility

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

4.7 Effects on ability to drive and use machines

Brigatinib 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 Brigatinib . **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 Brigatinib (N = 219) with ALK+ NSCLC who previously progressed on crizotinib. Patients were randomised in a 1:1 ratio to receive Brigatinib either 90 mg once daily continuously (90 mg regimen) or 180 mg once daily with 7day 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 (≥ 25%) reported in patients treated with Brigatinib 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 (≥ 2%) reported in patients treated with Brigatinib 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 (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 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 Brigatinib 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	Pneumoniaa Upper respiratory tract infection	
	Common		Pneumoniaa

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 decreased count
Metabolism and nutrition disorders	Very common	Hyperglycaemia Hyperinsulinaemiab Hypophosphataemia Decreased appetite Hypokalaemia Hypomagnesaemia Hyponatraemia Hypercalcaemia	
	Common		Hypophosphataemia Hyperglycaemia Hyponatraemia Hypokalaemia Decreased appeti te
Psychiatric disorders	Very common	Insomnia	
Nervous system disorders	Very common	Headachec Peripheral neuropathyd Dizziness	
	Common	Memory impairment Dysgeusia	Peripheral neuropathyd Headache c
Eye disorders	Very common	Visual disturbance e	
	Common		Visual disturbance
Cardiac disorders	Common	Tachycardiaf Electrocardiogram QT prolonged Bradycardiag Palpitations	
	Uncommon		Electrocardiogram QT prolonged
Vascular disorders	Very Common	Hypertension	Hypertension

Respiratory, thoracic and mediastinal disorders	Very Common	Cough Dyspnoeah	
	Common	Pneumonitisi	Pneumonitisi Dyspnoeah

Gastrointestinal disorders	Very common	Lipase increased Nausea Diarrhoeaj Amylase increased Vomiting Constipation Abdominal paink Dry mouth Stomatitisl	Lipase increased
	Common	Dyspepsia Flatulence	Amylase increased Abdominal paink
	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	Rashm Pruritus	
	Common	Dry skin Photosensitivity reaction	Rashm Photosensitivity reaction
	Uncommon		Dry skin
Musculoskeletal and connective tissue disorders	Very common	Blood CPK increased Myalgian 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	
General disorders and administration site conditions	Very common	Fatigueo Oedemap Pyrexia	
	Common	Pain Non-cardiac chest pain Chest discomfort	Fatigueo
	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 Brigatinib 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.

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 Brigatinib 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.

Bradycardia

In ALTA, bradycardia was reported in 4.5% of patients treated with Brigatinib 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.. Visual

disturbance

In ALTA, visual disturbance adverse reactions were reported in 18% of patients treated with Brigatinib 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.

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 Brigatinib 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 Brigatinib , 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 Brigatinib , 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.

Hyperglycemia

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

No patients had dose reductions due to hyperglycemia.

4.9 Overdose

There is no specific antidote for overdose with Brigatinib . In the event of an overdose, monitor the patient for adverse reactions 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 vivoviability 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 Brigatinib 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 exposureQT analysis suggested no concentration-dependent QTc interval prolongation.

Pediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Brigatinib in all subsets of the paediatric population in lung carcinoma (small cell and non-small cell carcinoma) **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 (Tmax) 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 Cmax of brigatinib at doses of 90 mg and 180 mg once daily was 552 and 1,452 ng/mL, respectively, and the corresponding AUC0-τ 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 Cmax 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 concentrationdependent. The blood-to-plasma concentration ratio is 0.69. In patients given brigatinib 180 mg once daily, the geometric mean apparent volume of distribution (Vz/F) 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 [14C]brigatinib to healthy subjects, Ndemethylation 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, Ndesmethyl 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 [14C]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 AUC0-INF was 37% higher in patients with severe hepatic impairment (Child-Pugh class C) as compared to healthy subjects with normal hepatic function.

Renal impairment

The pharmacokinetics of brigatinib is similar in patients with normal renal function and in patients with mild or moderate renal impairment (eGFR ≥ 30 mL/min) based on the results of population pharmacokinetic analyses. In a pharmacokinetic study, unbound AUC0-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 ≥ 90 mL/min, N = 8).

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 0.7times 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 Pregelatinized starch

Sodium Starch Glycolate

Ludipress

Magnesium Stearate

Colloidal Anhydrous Silica

Microcrystalline Cellulose

6.2 Incompatibilities Not applicable.

6.3 Shelf life

Brigatinib 180mg tablet

24 Months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Brigatinib 180mg tablet

Round wide mouth high density polyethylene (HDPE) bottles with foil induction seal liner closures, Containing 30 tablets, together with one HDPE bottle canister containing a molecular sieve desiccant. ,

. **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. Manufacturer & Marketing authorization holder

Beacon Pharmaceuticals Limited

Kathali, Bhaluka, Mayensingh, Bangladesh

8. Marketing in Pakistan by:

Himmel Pharmaceuticals (Pvt) Ltd,
Ground Floor, 6-Judicial Colony, Phase-1 (Ext) Shahrah Nazaria e
Pakistan, Lahore

9. Registration details:

Registration No. 122443

Date of Issuance of Registration Letter: 30 September, 2024