

CORE DATA SHEET 6.0

October 2017

ALECENSA, ALECENSARO

Alectinib

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Antineoplastic agent, Protein Kinase inhibitor

ATC Code: L01XE36

1.2 TYPE OF DOSAGE FORM

Hard capsule

1.3 ROUTE OF ADMINISTRATION

Oral

1.4 STERILE / RADIOACTIVE STATEMENT

Not applicable

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Alectinib

Each hard capsule contains: Alectinib 150 mg (equivalent to 161.3 mg alectinib hydrochloride).

Excipients: lactose monohydrate, hydroxypropylcellulose, sodium lauryl sulfate, carboxymethylcellulose calcium, and magnesium stearate

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

Alecensa as monotherapy is indicated for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

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Alecensa is indicated for the treatment of patients with ALK-positive, locally advanced or metastatic NSCLC who have progressed on or are intolerant to crizotinib.

2.2 DOSAGE AND ADMINISTRATION

General

A validated ALK assay is required for the selection of ALK-positive NSCLC patients. ALK-positive NSCLC status should be established prior to initiation of Alecensa therapy in first-line.

Alecensa hard capsules should be taken with food, swallowed whole and must not be opened or dissolved.

The recommended dose of Alecensa is 600 mg (four 150 mg capsules) given orally, twice daily (total daily dose of 1200 mg) (*see section 3.2 Pharmacokinetic Properties*).

Patients with underlying severe hepatic impairment should receive a dose of 450 mg given orally twice daily (total daily dose of 900 mg) (*see sections 2.2.1 Special Dosing Instructions and 3.2.5 Pharmacokinetics in Special Populations*).

Duration of Treatment

It is recommended that patients are treated with Alecensa until disease progression or unmanageable toxicity.

Delayed or Missed Doses

If a planned dose of Alecensa is missed, patients can make up that dose unless the next dose is due within 6 hours. If vomiting occurs after taking a dose of Alecensa, patients should take the next dose at the scheduled time.

Dose Modifications

Management of adverse events may require temporary interruption, dose reduction, or discontinuation of treatment with Alecensa. The dose of Alecensa should be reduced in steps of 150 mg twice daily based on tolerability. Alecensa treatment should be permanently discontinued if patients are unable to tolerate the 300 mg twice daily dose.

Table 1 below gives general dose modification advice for Alecensa.

Table 1 Dose Reduction Schedule

Dose reduction schedule	Dose level
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Dose	600 mg twice daily
First dose reduction	450 mg twice daily
Second dose reduction	300 mg twice daily

Table 2 Dose modification advice for specified Adverse Drug Reactions (*see sections 2.4.1 Warnings and Precautions and 2.6 Undesirable Effects*):

Grade	Alecensa Treatment
Interstitial Lung Disease (ILD)/Pneumonitis (all Grades)	Immediately interrupt and permanently discontinue if no other potential causes of ILD/pneumonitis have been identified
ALT or AST elevation of Grade ≥ 3 (> 5 times ULN) with total bilirubin ≤ 2 times ULN	Temporarily withhold until recovery to baseline or \leq Grade 1 (≤ 3 times ULN), then resume at reduced dose (see Table 1)
ALT or AST elevation of Grade ≥ 2 (> 3 times ULN) with total bilirubin elevation > 2 times ULN in the absence of cholestasis or hemolysis	Permanently discontinue Alecensa
Bradycardia ^a Grade 2 or Grade 3 (symptomatic, may be severe and medically significant, medical intervention indicated)	Temporarily withhold until recovery to \leq Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to \leq Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose (see Table 1) upon recovery to \leq Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm.
Bradycardia ^a Grade 4 (life-threatening)	Permanently discontinue if no contributing

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consequences, urgent intervention indicated)	concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at reduced dose (see Table 1) upon recovery to \leq Grade 1 (asymptomatic) bradycardia or to a heart rate of \geq 60 bpm, with frequent monitoring as clinically indicated. Permanently discontinue in case of recurrence.
CPK elevation > 5 times ULN	Temporarily withhold until recovery to baseline or to \leq 2.5 times ULN, then resume at same dose
CPK elevation >10 times ULN or second occurrence of CPK elevation of > 5 times ULN	Temporarily withhold until recovery to baseline or to \leq 2.5 times ULN, then resume at reduced dose as per Table 1

ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal ^a Heart rate less than 60 beats per minute (bpm)

2.2.1 Special Dosage Instructions

Pediatric use

The safety and efficacy of Alecensa in children and adolescents (<18 years) have not been studied.

Geriatric use

No dose adjustment of Alecensa is required in patients \geq 65 years of age.

Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. Alecensa has not been studied in patients with severe renal impairment, however since alectinib elimination via the kidney is negligible, no dose adjustment is required in patients with severe renal impairment (*see sections 2.5 Use in Special Populations and 3.2.5 Pharmacokinetics in Special Populations*).

Hepatic Impairment

No dose adjustment is required in patients with underlying mild or moderate hepatic impairment. Patients with underlying severe hepatic impairment should receive a dose of 450 mg given orally twice daily (total daily dose of 900 mg) (*see section 3.2.5 Pharmacokinetics in Special Populations*).

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2.3 CONTRAINDICATIONS

Alecensa is contraindicated in patients with a known hypersensitivity to alectinib or any of the excipients.

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

Interstitial lung disease (ILD)/Pneumonitis

Cases of ILD/pneumonitis have been reported in clinical trials with Alecensa (*see section 2.6.1 Undesirable Effects*). Patients should be monitored for pulmonary symptoms indicative of pneumonitis. Alecensa should be immediately interrupted in patients diagnosed with ILD/pneumonitis and should be permanently discontinued if no other potential causes of ILD/pneumonitis have been identified (*see section 2.2 Dosage and Administration*).

Hepatotoxicity

Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) greater than 5 times the upper limit of normal (ULN) as well as bilirubin elevations of more than 3 times the ULN occurred in patients in pivotal clinical trials with Alecensa (*see section 2.6.1 Undesirable Effects*). The majority of these events occurred during the first 3 months of treatment. In the pivotal Alecensa clinical trials it was reported that three patients with Grade 3-4 AST/ALT elevations had drug induced liver injury. Concurrent elevations in ALT or AST greater than or equal to three times the ULN and total bilirubin greater than or equal to two times the ULN, with normal alkaline phosphatase, occurred in 1 patient treated in Alecensa clinical trials.

Liver function, including ALT, AST, and total bilirubin should be monitored at baseline and then every 2 weeks during the first 3 months of treatment, and then periodically, since events may occur later than 3 months, with more frequent testing in patients who develop transaminase and bilirubin elevations. Based on the severity of the adverse drug reaction, withhold Alecensa and resume at a reduced dose, or permanently discontinue Alecensa as described in Table 2 (*see section 2.2 Dosage and Administration*).

Severe Myalgia and Creatine Phosphokinase (CPK) elevation

Myalgia or musculoskeletal pain was reported in patients in pivotal trials with Alecensa, including Grade 3 events.

Elevations of CPK occurred in pivotal trials with Alecensa, including Grade 3 events. Median time to Grade 3 CPK elevation was 14 days in the pivotal phase II trials (NP28761, NP28673). Median time to Grade 3 CPK elevation was 27.5 days in the pivotal phase III clinical trial (BO28984) (*see section 2.6.1. Undesirable Effects*)

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Advise patients to report any unexplained muscle pain, tenderness, or weakness. Assess CPK levels every two weeks for the first month of treatment and as clinically indicated in patients reporting symptoms. Based on the severity of the CPK elevation, withhold Alecensa, then resume or reduce dose (*see section 2.2 Dosage and Administration*).

Bradycardia

Symptomatic bradycardia can occur with Alecensa (*see section 2.6 Undesirable Effects*). Heart rate and blood pressure should be monitored as clinically indicated. Dose modification is not required in case of asymptomatic bradycardia (*see section 2.2 Dosage and Administration*). If patients experience symptomatic bradycardia or life-threatening events, concomitant medications known to cause bradycardia, as well as anti-hypertensive medications should be evaluated and Alecensa treatment should be adjusted as described in Table 2 (*see sections 2.2 Dosage and Administration and 2.8 Interactions with other Medicinal Products and other Forms of Interaction, P-gp and BCRP substrates*).

Photosensitivity

Photosensitivity to sunlight has been reported with Alecensa administration (*see section 2.6.1 Undesirable Effects*). Patients should be advised to avoid prolonged sun exposure while taking Alecensa and for at least 7 days after discontinuation of treatment. Patients should also be advised to use a broad-spectrum Ultraviolet A (UVA)/Ultraviolet B (UVB) sun screen and lip balm (SPF ≥ 50) to help protect against potential sunburn.

Embryo-fetal toxicity

Alecensa may cause fetal harm when administered to a pregnant woman. When administered to pregnant rats and rabbits, alectinib caused embryo-fetal toxicity. Female patients of child-bearing potential, or women of child-bearing potential who are partners of male patients receiving Alecensa, must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of Alecensa (*see section 2.5 Use in Special Populations*).

2.4.2 Drug Abuse and Dependence

Not applicable.

2.4.3 Ability to Drive and Use Machines

No studies on the effects on the ability to drive and to use machines have been performed.

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Females and Males of Reproductive Potential

Contraception

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Female patients of child-bearing potential, or women of child-bearing potential who are partners of male patients receiving Alecensa, must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of Alecensa.

2.5.2 Pregnancy

Women of childbearing potential must be advised to avoid pregnancy while on Alecensa. No clinical studies of Alecensa in pregnant women have been performed. Based on its mechanism of action, Alecensa may cause fetal harm when administered to a pregnant woman.

Female patients or women who are partners of male patients receiving Alecensa, who become pregnant while taking Alecensa or during the 3 months following the last dose of Alecensa must contact their doctor and should be advised of the potential harm to the fetus.

Animal data

In animal studies, alectinib caused embryo-fetal toxicity (*see section 3.3 Nonclinical Safety*).

Labor and Delivery

The safe use of Alecensa during labor and delivery has not been established.

2.5.3 Lactation

It is not known whether Alecensa is excreted in human breast milk. No studies have been conducted to assess the impact of Alecensa on milk production or its presence in breast milk. As many drugs are excreted in human milk and because of the potential harm to the infant, mothers should be advised against breastfeeding while receiving Alecensa.

2.5.4 Pediatric Use

Safety and efficacy in pediatric patients below the age of 18 have not been established.

2.5.5 Geriatric Use

see section 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations.

2.5.6 Renal Impairment

see sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations

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2.5.7 Hepatic Impairment

see sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials

For the clinical development program of Alecensa as a whole, an estimated total of 928 patients have received Alecensa and 203 patients have received blinded Alecensa. The safety of Alecensa has been evaluated in 253 patients in pivotal phase II clinical trials (NP28761, NP28673) with ALK-positive non-small cell lung cancer (NSCLC) treated with the recommended dose of 600 mg twice daily. The median duration of exposure to Alecensa was 11 months (range 0-35 months). The safety of Alecensa was also evaluated in 152 patients with ALK-positive NSCLC treated with a dose of 600 mg twice daily in the phase III clinical trial BO28984. The median duration of exposure to Alecensa was 17.9 months.

The most common adverse drug reactions ($\geq 20\%$) were constipation (36%), edema (34% including peripheral, generalized, eyelid, periorbital); myalgia (31% including myalgia and musculoskeletal pain), nausea (22%), increased bilirubin (21% including increased blood bilirubin, hyperbilirubinemia and increased bilirubin conjugated), anemia (20%, including anemia and hemoglobin decreased), and rash (20%, including rash, rash maculopapular, dermatitis acneiform, erythema, rash generalized, rash papular, rash pruritic and rash macular).

Table 3 lists the adverse drug reactions (ADRs) occurring in patients who received Alecensa in clinical trials (NP28761, NP28673) and phase III clinical trial BO28984. Adverse drug reactions from clinical trials are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$).

Table 3 – Adverse drug reactions occurring in patients treated with Alecensa in pivotal phase II clinical trials (NP28761, NP28673) and phase III trial BO28984

Adverse Reactions (MedDRA)	Alecensa		
	N=253 (NP28761, NP28673) /N=152 (BO28984)		
System Organ Class	All Grades (%)	Grade 3 – 4 (%)	Frequency Category (All Grades)

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Gastrointestinal Disorders			
Constipation	36	0	very common
Nausea	22	0.7 [#]	very common
Diarrhea	18	1.2	very common
Vomiting	13	0.4	very common
Stomatitis ^{#1}	3.3 [#]	0 [#]	common
General Disorders and Administration Site Conditions			
Edema ²	34	0.8	very common
Musculoskeletal and Connective Tissue Disorders			
Myalgia ³	31	1.2	very common
Increased Blood Creatine Phosphokinase	13	3.6	very common
Skin and Subcutaneous Tissue Disorders			
Rash ⁴	20	0.7 [#]	very common
Photosensitivity Reaction	12	0.7 [#]	very common
Nervous System Disorders			
Dysgeusia ^{#5}	3.3 [#]	0.7 [#]	common
Hepatobiliary Disorders			
Increased Bilirubin ⁶⁴	21 [#]	3.3 [#]	very common
Increased AST	16	5.3 [#]	very common
Increased ALT	15 [#]	4.6 [#]	very common
Drug-Induced Liver Injury ⁷	0.8	0.8	uncommon
Blood and Lymphatic System Disorders			

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Anemia ⁸	20 [#]	4.6 [#] ...	very common
Eye Disorders			
Vision Disorders ⁹	12	0	very common
Cardiac Disorders			
Bradycardia ¹⁰	11 [#]	0	very common
Investigations			
Weight increased [#]	9.9 [#]	0.7 [#]	common
Renal and Urinary Disorders			
Increased Blood Creatinine	7.9 [#]	1.3 ^{#*}	common
Acute kidney injury [#]	2.6 [#]	2.6 ^{#*}	common
Respiratory, Thoracic and Mediastinal Disorders			
Interstitial Lung Disease/ Pneumonitis	1.3 [#]	0.4	common

* Includes one Grade 5 event

[#] Event and/or rate reported in trial BO28984; N=152 patients treated with Alecensa; remainder of events and/or rates reported in trials NP28761, NP28673; N=253 patients treated with Alecensa

¹ includes cases of stomatitis and mouth ulceration

² includes cases of peripheral edema, edema, generalized edema, eyelid edema, periorbital edema

³ includes cases of myalgia and musculoskeletal pain

⁴ includes cases of rash, rash maculo-papular, dermatitis acneiform, erythema, rash generalized, rash papular, rash pruritic, and rash macular

⁵ includes cases of dysgeusia and hypogeusia

⁶ includes cases of increased blood bilirubin, hyperbilirubinemia and increased bilirubin conjugated

⁷ includes one patient with reported MedDRA term of drug-induced liver injury as well as one patient with reported Grade 4 increased AST and ALT who had documented drug-induced liver injury by liver biopsy.

⁸ includes cases of anemia and hemoglobin decreased

⁹ includes cases of blurred vision, visual impairment, vitreous floaters, reduced visual acuity, asthenopia, and diplopia

¹⁰ includes cases of bradycardia and sinus bradycardia

Further information on selected adverse drug reactions:

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The safety profile of Alecensa was generally consistent across the phase III clinical trial (BO28984) and the pivotal phase II trials (NP28761, NP28673); however, relevant differences between studies are described below.

Interstitial Lung Disease (ILD)/pneumonitis

Severe ILD/pneumonitis occurred in patients treated with Alecensa. In the pivotal phase II clinical trials (NP28761, NP28673), 1 out of 253 patients treated with Alecensa (0.4%) had an ILD event, which was Grade 3, leading to withdrawal from Alecensa treatment. There were no fatal cases of ILD in any of the clinical trials.

Hepatotoxicity

In the pivotal phase II clinical trials (NP28761, NP28673) two patients with Grade 3-4 AST/ALT elevations had documented drug induced liver injury by liver biopsy. Adverse reactions of increased AST and ALT levels (16% and 14% respectively) were reported in patients treated with Alecensa in pivotal phase II clinical trials (NP28761, NP28673). The majority of these events were of Grade 1 and 2 intensity, and events of Grade ≥ 3 were reported in 2.8% and 3.2% of the patients, respectively. The events generally occurred during the first 3 months of treatment, were usually transient and resolved upon temporary interruption of Alecensa treatment (reported for 1.2% and 3.2% of the patients, respectively) or dose reduction (1.6% and 0.8%, respectively). In 1.2% and 1.6% of the patients, AST and ALT elevations, respectively, led to withdrawal from Alecensa treatment.

Adverse reactions of bilirubin elevations were reported in 17% of the patients treated with Alecensa in pivotal phase II clinical trials (NP28761, NP28673). The majority of the events were of Grade 1 and 2 intensity; Grade 3 events were reported in 3.2% of the patients. The events generally occurred during the first 3 months of treatment, were usually transient and resolved upon temporary interruption of Alecensa treatment (4.7% of the patients) or dose reduction (2.8%). In 4 patients (1.6%), bilirubin elevations led to withdrawal from Alecensa treatment.

Concurrent elevations in ALT or AST greater than or equal to three times the ULN and total bilirubin greater than or equal to two times the ULN, with normal alkaline phosphatase, occurred in 1 patient treated in Alecensa clinical trials.

Bradycardia

Cases of bradycardia (7.9%) have been reported in patients treated with Alecensa in pivotal phase II clinical trials (NP28761, NP28673); all cases were of Grade 1 or 2 intensity. There were 44 of 221 patients (20%) treated with Alecensa who had post-dose heart rate values below 50 beats per minutes [bpm].

Severe Myalgia and CPK elevation

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Cases of myalgia (31%) including myalgia events (25%) and musculoskeletal pain (7.5%) have been reported in patients treated with Alecensa in pivotal phase II clinical trials (NP28761, NP28673). The majority of events were Grades 1 or 2 and three patients (1.2%) had a Grade 3 event. Dose modifications due to these events were only required for two patients (0.8%). Elevations of CPK occurred in 46% of 219 patients with CPK laboratory data available in pivotal phase II clinical trials (NP28761, NP28673) with Alecensa. The incidence of Grade 3 elevations of CPK was 5.0%. Median time to Grade 3 CPK elevation was 14 days in the pivotal phase II trials (NP28761, NP28673). Median time to Grade 3 CPK elevation was 27.5 days in the pivotal phase III clinical trial (BO28984). Dose modifications for elevation of CPK occurred in 4.0% of patients.

Laboratory Abnormalities

The following table displays treatment-emergent shifts in laboratory abnormalities occurring in patients treated with Alecensa in phase II clinical trials (NP28761, NP28673) and phase III trial BO28984.

Table 4 Alecensa Treatment-emergent shifts in key laboratory abnormalities

Parameter	Alectinib N= 250*/N=152 [#]	
	All Grade (%)	Grade 3 -4(%) ^o
Chemistry		
Increased Blood Creatinine**	38 [#]	3.4 [#]
Increased AST	53*	6.2 [#]
Increased ALT	40 [#]	6.1 [#]
Increased Blood Creatine Phosphokinase	46*	5.0*
Increased Blood Bilirubin	53 [#]	5.5 [#]
Hematology		
Decreased Hemoglobin	62 [#]	6.8 [#]

AST - Aspartate Aminotransferase, ALT - Alanine Aminotransferase

Note: Laboratory abnormalities were based on the normal ranges of the NCI CTCAE.

* Rate reported in NP28761 and NP28673 studies, N= 219 for Creatine Phosphokinase.

** Only patients with creatinine increases based on ULN definition (CTCAE grading).

[#] Rate reported in trial BO28984; Patients with missing baseline and/or no post-baseline lab assessments were excluded from analyses; N=147 for Blood Creatinine, ALT and Hemoglobin; N=145 for AST; N=146 for Blood Bilirubin.

^o No Grade 5 laboratory abnormalities were reported.

2.6.2 Postmarketing Experience

The adverse drug reaction of increased alkaline phosphatase was reported with Alecensa in the post marketing period. Cases of increased alkaline phosphatase have been reported

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in Alecensa clinical trials (7.5% in patients treated with Alecensa in pivotal phase II clinical trials (NP28761, NP28673)).

2.7 OVERDOSE

There is no experience with overdosage in clinical trials NP28761, NP28673 and BO28984. Patients who experience overdose should be closely supervised and supportive care instituted. There is no specific antidote for overdose with Alecensa.

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Effects of alectinib on others drugs

CYP substrates

In vitro studies indicate that neither alectinib nor its major active metabolite (M4) inhibits CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations. Alectinib and M4 show weak time-dependent inhibition of CYP3A4. *In vitro*, alectinib exhibits a weak induction potential of CYP3A4 and CYP2B6 at clinical concentrations.

Results from a clinical drug-drug interaction study in ALK-positive NSCLC patients demonstrated that multiple doses of alectinib had no influence on the exposure of midazolam, a sensitive CYP3A substrate. Therefore, no dose adjustment is required for co-administered CYP3A substrates.

Although *in vitro* studies indicate that alectinib is an inhibitor of CYP2C8, physiologically based pharmacokinetic (PBPK) modeling supports that at clinically relevant concentrations alectinib does not have the potential to increase plasma concentrations of co-administered substrates of CYP2C8.

P-gp and BCRP substrates

In vitro, alectinib and M4 are inhibitors of the efflux transporters P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). Therefore, alectinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp or BCRP transporters (the increase in exposure is not expected to be more than 2-fold). When alectinib is co-administered with P-gp or BCRP substrates with narrow therapeutic index (e.g. digoxin, dabigatran, methotrexate), appropriate monitoring is recommended.

Effects of other drugs on alectinib

Based on *in vitro* data, CYP3A4 is the primary enzyme mediating the metabolism of both alectinib and its major active metabolite M4, and CYP3A contributes to 40% – 50% of

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total hepatic metabolism. M4 has shown similar *in vitro* potency and activity to alectinib against ALK.

CYP3A inducers

Co-administration of multiple oral doses of 600 mg rifampicin once daily, a strong CYP3A inducer, with a single oral dose of 600 mg alectinib exhibited a minor effect on combined exposure of alectinib and M4 (geometric mean ratio with/without rifampicin [90% confidence interval]: C_{max} : 0.96 [0.88 – 1.05], AUC_{inf} : 0.82 [0.74 – 0.90]). Therefore, no dose adjustments are required when Alecensa is co-administered with CYP3A inducers.

CYP3A inhibitors

Co-administration of multiple oral doses of 400 mg posaconazole twice daily, a strong CYP3A inhibitor, with a single oral dose of 300 mg alectinib had a minor effect on combined exposure of alectinib and M4 (geometric mean ratio with/without posaconazole [90% confidence interval]: C_{max} : 0.93 [0.81 – 1.08], AUC_{inf} : 1.36 [1.24 – 1.49]). Therefore, no dose adjustments are required when Alecensa is co-administered with CYP3A inhibitors.

Medicinal products that increase gastric pH

Although the aqueous solubility of alectinib *in vitro* is pH dependent, a dedicated clinical drug-drug interaction study with 40 mg esomeprazole once daily, a proton pump inhibitor, demonstrated no clinically relevant effect on the combined exposure of alectinib and M4. Therefore, no dose adjustments are required when Alecensa is co-administered with proton pump inhibitors or other drugs which raise gastric pH (e.g. H2 receptor antagonists or antacids).

Effect of transporters on alectinib disposition

Based on *in vitro* data, alectinib is not a substrate of P-gp. Alectinib and M4 are not substrates of BCRP or Organic anion-transporting polypeptide (OATP) 1B1/B3. In contrast, M4 is a substrate of P-gp. Alectinib inhibits P-gp, and therefore, it is not expected that co-medication with P-gp inhibitors has a relevant effect on M4 exposure.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

3.1.1 Mechanism of Action

Alectinib is a highly selective and potent ALK and RET tyrosine kinase inhibitor. In nonclinical studies, inhibition of ALK tyrosine kinase activity led to blockage of

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downstream signalling pathways including STAT 3 and PI3K/AKT and induces tumor cell death (apoptosis).

Alectinib demonstrated *in vitro* and *in vivo* activity against mutant forms of the ALK enzyme, including mutations responsible for resistance to crizotinib. The major metabolite of alectinib (M4) has shown similar *in vitro* potency and activity.

Based on nonclinical data, alectinib is not a substrate of p-glycoprotein (P-gp) or Breast Cancer Resistance Protein (BCRP), which are both efflux transporters in the blood brain barrier, and is therefore able to distribute into and be retained within the central nervous system. Alectinib induced tumor regression in nonclinical mouse xenograft models, including antitumor activity in the brain, and prolonged survival in intracranial tumor animal models.

3.1.2 Clinical / Efficacy Studies

ALK positive non-small cell lung cancer

Treatment-naïve patients

The safety and efficacy of Alecensa were studied in a global randomized Phase III open label clinical trial (BO28984) in ALK-positive NSCLC patients who were treatment naïve [39, 40]. Central testing for ALK protein expression positivity of tissue samples from all patients by Ventana anti-ALK (D5F3) immunohistochemistry (IHC) was required before randomization into the study.

A total of 303 patients were included in the Phase III trial, 151 patients randomized to the crizotinib arm and 152 patients randomized to the Alecensa arm receiving Alecensa orally, at the recommended dose of 600 mg twice daily.

ECOG PS (0/1 vs. 2), race (Asian vs. non-Asian), and CNS metastases at baseline (yes vs. no) were stratification factors for randomization. The primary endpoint of the trial was to demonstrate superiority of Alecensa versus crizotinib based on Progression Free survival (PFS) as per investigator assessment using RECIST 1.1. Baseline demographic and disease characteristics for Alecensa were median age 58 years (54 years for crizotinib), 55% female (58% for crizotinib), 55% non-Asian (54% for crizotinib), 61% with no smoking history (65% for crizotinib), 93% ECOG PS of 0 or 1 (93% for crizotinib), 97% Stage IV disease (96% for crizotinib), 90% adenocarcinoma histology (94% for crizotinib), 40% CNS metastases at baseline (38% for crizotinib) and 17% having received prior CNS radiation (14% for crizotinib).

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The trial met its primary endpoint at the primary analysis. Efficacy data are summarized in Table 5 and the Kaplan-Meier curves for investigator and IRC-assessed PFS are shown in Figures 1 and 2.

Table 5 Summary of efficacy results from study BO28984

	Crizotinib N=151	Alecensa N=152
Median duration of follow-up (months)	17.6 (range 0.3 – 27.0)	18.6 (range 0.5 – 29.0)
Primary Efficacy Parameter		
PFS (INV) Number of patients with event n (%) Median (months) [95% CI]	102 (68%) 11.1 [9.1; 13.1]	62 (41%) NE [17.7; NE]
HR [95% CI] Stratified log-rank p-value	0.47 [0.34, 0.65] p < 0.0001	
Secondary efficacy parameters		
PFS (IRC)* Number of patients with event n (%) Median (months) [95% CI]	92 (61%) 10.4 [7.7; 14.6]	63 (41%) 25.7 [19.9; NE]
HR [95% CI] Stratified log-rank p-value	0.50 [0.36; 0.70] p < 0.0001	
Time to CNS progression (IRC)* (without prior systemic PD**) Number of patients with event n (%)	68 (45%)	18 (12%)
Cause-Specific HR [95% CI] Stratified log-rank p-value	0.16 [0.10; 0.28] p < 0.0001	
12-month cumulative incidence of CNS progression (IRC) % (95% CI)	41.4% [33.2; 49.4]	9.4% [5.4; 14.7]
ORR (INV)*, *** Responders n (%) [95% CI]	114 (75.5%) [67.8; 82.1]	126 (82.9%) [76.0; 88.5]
Overall survival* Number of patients with event n (%) Median (months) [95% CI]	40 (27%) NE [NE; NE]	35 (23%) NE [NE; NE]
HR	0.76	

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[95% CI]	[0.48; 1.20]	
Duration of response (INV)	N=114	N=126
Median (months)	11.1	NE
95 % CI	[7.9; 13.0]	[NE; NE]
CNS-ORR in patients with measurable CNS metastases at baseline	N=22	N=21
CNS responders n (%)	11 (50.0%)	17 (81.0%)
[95% CI]	[28.2; 71.8]	[58.1; 94.6]
CNS-CR n (%)	1 (5%)	8 (38%)
CNS-DOR , median (months)	5.5	17.3
95% CI	[2.1, 17.3]	[14.8, NE]
CNS-ORR in patients with measurable and non-measurable CNS metastases at baseline (IRC)	N=58	N=64
CNS responders n (%)	15 (25.9%)	38 (59.4%)
[95% CI]	[15.3%; 39.0%]	[46.4%; 71.5%]
CNS-CR n (%)	5 (9%)	29 (45%)
CNS-DOR , median (months)	3.7	NE
95% CI	[3.2, 6.8]	[17.3, NE]

*Key secondary endpoints part of the hierarchical testing

** Competing risk analysis of CNS progression, systemic progression and death as competing events

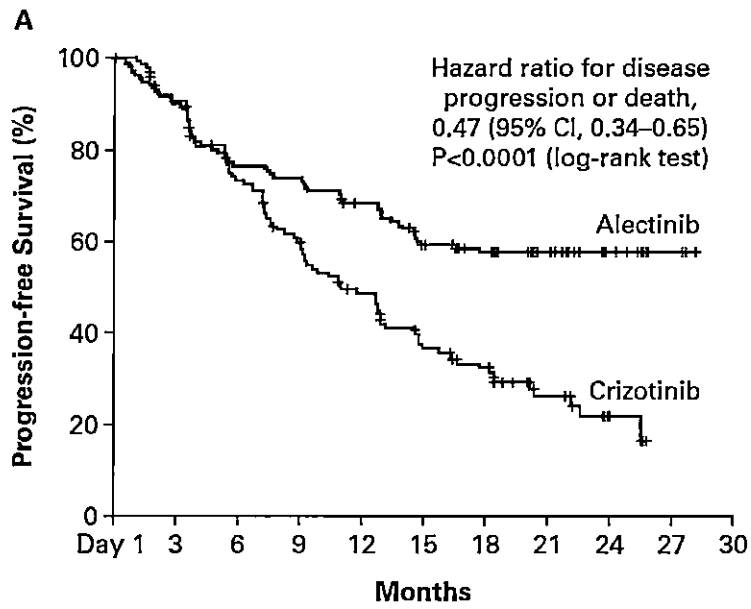
*** 2 patients in the crizotinib arm and 6 patients in the alectinib arm had CR

CI = confidence interval; CNS = central nervous system; CR = complete response; DOR = duration of response; HR = hazard ratio; IRC = Independent Review Committee; INV = investigator; NE = not estimable; ORR = objective response rate; PFS = progression-free survival

The magnitude of PFS benefit was consistent for patients with CNS metastases at baseline (HR=0.40, 95%CI: 0.25-0.64, median PFS for Alecensa = NE, 95% CI: 9.2-NE, median PFS for crizotinib = 7.4 months, 95%CI: 6.6-9.6) and without CNS metastases at baseline (HR = 0.51, 95%CI: 0.33-0.80, median PFS for Alecensa = NE, 95% CI: NE, NE, median PFS for crizotinib = 14.8 months, 95%CI:10.8-20.3), indicating benefit of Alecensa over crizotinib in both subgroups.

Figure 1: Kaplan Meier Plot of INV Assessed PFS in BO28984

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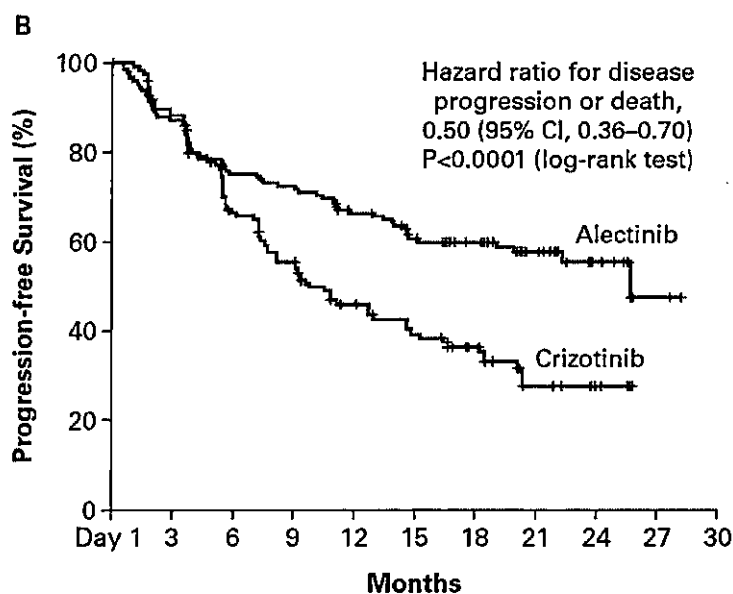


No. at Risk

Crizotinib	151	132	104	84	65	46	35	16	5	
Alectinib	152	135	113	109	97	81	67	35	15	3

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Figure 2: Kaplan Meier Plot of IRC Assessed PFS in BO28984



No. at Risk

Crizotinib	151	128	92	74	57	46	33	12	4	
Alectinib	152	132	112	108	95	83	69	35	15	2

Crizotinib pre-treated patients

The safety and efficacy of Alecensa in ALK-positive NSCLC patients pre-treated with crizotinib were studied in two Phase I/II clinical trials (NP28761 and NP28673).

Study NP28761 was a Phase I/II single arm, multicenter study conducted in patients with ALK positive advanced NSCLC who have previously progressed on crizotinib treatment. In addition to crizotinib, patients may have received previous treatment with chemotherapy. A total of 87 patients were included in the phase II part of the study and received Alecensa orally, at the recommended dose of 600 mg twice daily.

The primary endpoint was to evaluate the efficacy of Alecensa by Objective Response Rate (ORR) as per central Independent Review Committee (IRC) assessment using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Patient demographics were consistent with that of a NSCLC ALK positive population. The demographic characteristics of the overall study population were 84% Caucasian, 8% Asian, 55% females and a median age of 54 years. The majority of patients had no history of smoking (62%). The ECOG (Eastern Cooperative Oncology Group) performance status at baseline was 0 or 1 in 90% of patients and 2 in 10% of patients. At the time of entry in the study, 99% of patients had stage IV disease, 60% had brain

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metastases and in 94% of patients tumors were classified as adenocarcinoma. Among patients included in the study, 26% had previously progressed on crizotinib treatment only, and 74% had previously progressed on crizotinib and chemotherapy treatment.

Table 6 Summary of efficacy from NP28761 study

	NP28761 Alecensa 600 mg twice daily N=87
Median duration of follow-up (months)	17 (range 1 – 29)
Primary Efficacy Parameters	
ORR (IRC) in RE population Responders N (%) [95% CI]	N = 67 ^a 35 (52.2%) [39.7%, 64.6%]
Secondary Efficacy Parameters	
DOR (IRC) Number of patients with events N (%) Median (months) [95% CI]	N = 35 20 (57.1%) 14.9 [6.9, NE]
PFS (IRC) Number of patients with events N (%) Median duration (months) [95% CI]	N = 87 58 (66.7) 8.2 [6.3, 12.6]
Exploratory Efficacy Parameters	
DCR (IRC) in RE Population ^b CR+PR+SD ^c [95% CI]	N = 67 ^a 53 (79.1%) [67.4%, 88.1%]

CI = confidence interval; DOR = duration of response; DCR = disease control rate; IRC = independent review committee; NE = not estimable; ORR = Objective Response Rate; PFS = progression free survival
 RE = response evaluable

^a 20 patients did not have measurable disease at baseline according to the IRC and were not included in the IRC response evaluable population.

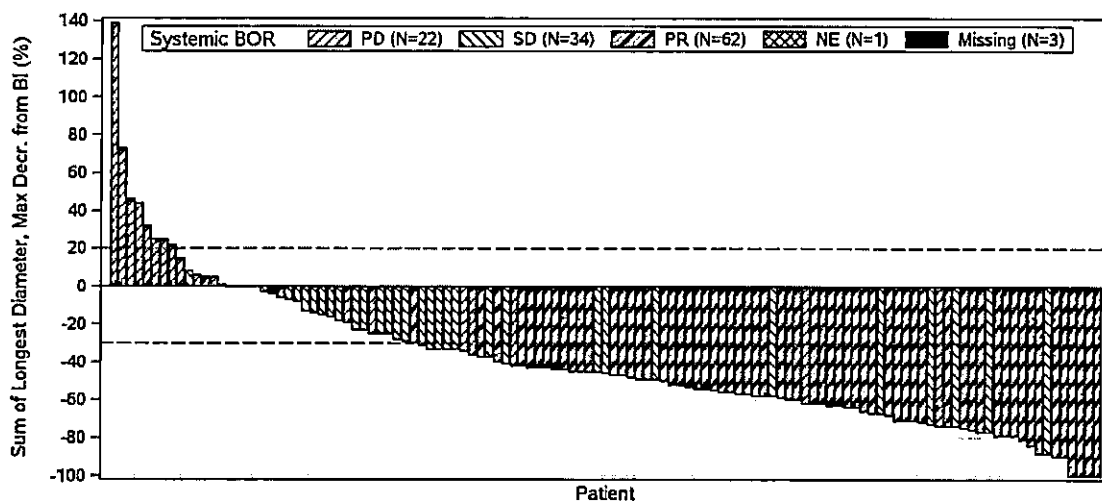
^b Exploratory analysis defined after database lock

^c DCR calculated including all patients who achieved a Best Overall Response (BOR) of SD (minimum duration of 5 weeks as per IRC Charter)

As shown in the waterfall plot in Figure 3, most patients experienced tumour shrinkage of their defined target lesions, as assessed by the IRC according to RECIST 1.1.

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Figure 3 Waterfall plot of target lesions sum of longest diameters best change from baseline shaded by best overall response (IRC) from NP28761 study



BOR= Best overall response, PD = progressive disease, SD = stable disease, PR = partial response, NE = not estimable.

Quality of life (QoL)

Of the QoL items analysed (QLQ-C30 and QLQ-LC13), clinically meaningful improvements (change from baseline of ≥ 10 points) were observed in the Global Health Status, Emotional Functioning, Social Functioning, Fatigue, and Pain subscales.

Study NP28673 was a Phase I/II single arm, international, multicenter study conducted in patients with ALK-positive advanced NSCLC who have previously progressed on crizotinib. In addition to crizotinib, patients may have received previous treatment with chemotherapy. A total of 138 patients were included in the phase II part of the study and received Alecensa orally, at the recommended dose of 600 mg twice daily.

The primary endpoint was to evaluate the efficacy of Alecensa by ORR as per central IRC assessment using RECIST 1.1 in the overall population (with and without prior exposure of cytotoxic chemotherapy treatments). The co-primary endpoint was to evaluate the ORR as per central IRC assessment using RECIST 1.1 in patients with prior exposure of cytotoxic chemotherapy treatments.

Patient demographics were consistent with that of a NSCLC ALK positive population. The demographic characteristics of the overall study population were 67% Caucasian, 26% Asian, 56% females and the median age was 52 years. The majority of patients had no history of smoking (70%). The ECOG performance status at baseline was 0 or 1 in 91% of patients and 2 in 9% of patients. At the time of entry in the study, 99% of patients had stage IV disease, 61% had brain metastases and in 96% of patients tumors

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were classified as adenocarcinoma. Among patients included in the study, 20% had previously progressed on crizotinib treatment only, and 80% had previously progressed on crizotinib and chemotherapy treatment.

Table 7 Summary of efficacy from NP28673 study

	NP28673 Alecensa 600 mg twice daily N=138
Median duration of follow-up (months)	21 (range 1 – 30)
Primary Efficacy Parameters	
ORR (IRC) in RE population Responders N (%) [95% CI]	N=122 ^a 62 (50.8%) [41.6%, 60.0%]
ORR (IRC) in Patients Pre-Treated with Chemotherapy Responders N (%) [95% CI]	N = 96 43 (44.8%) [34.6%, 55.3%]
Secondary Efficacy Parameters	
DOR (IRC) Number of patients with events N (%) Median (months) [95% CI]	N = 62 36 (58.1%) 15.2 [11.2, 24.9]
PFS (IRC) Number of patients with events N (%) Median duration (months) [95% CI]	N = 138 98 (71.0%) 8.9 [5.6, 12.8]
Exploratory Efficacy Parameter	
DCR (IRC) in RE Population ^b CR + PR + SD ^c [95% CI]	N = 122 ^a 96 (78.7%) [70.4%, 85.6%]

CI = confidence interval; DOR = duration of response; DCR = disease control rate; IRC = independent review committee; NE = not estimable; ORR = Objective Response Rate; PFS = progression free survival; RE = response evaluable

^a 16 patients did not have measurable disease at baseline according to the IRC and were not included in the IRC response evaluable population.

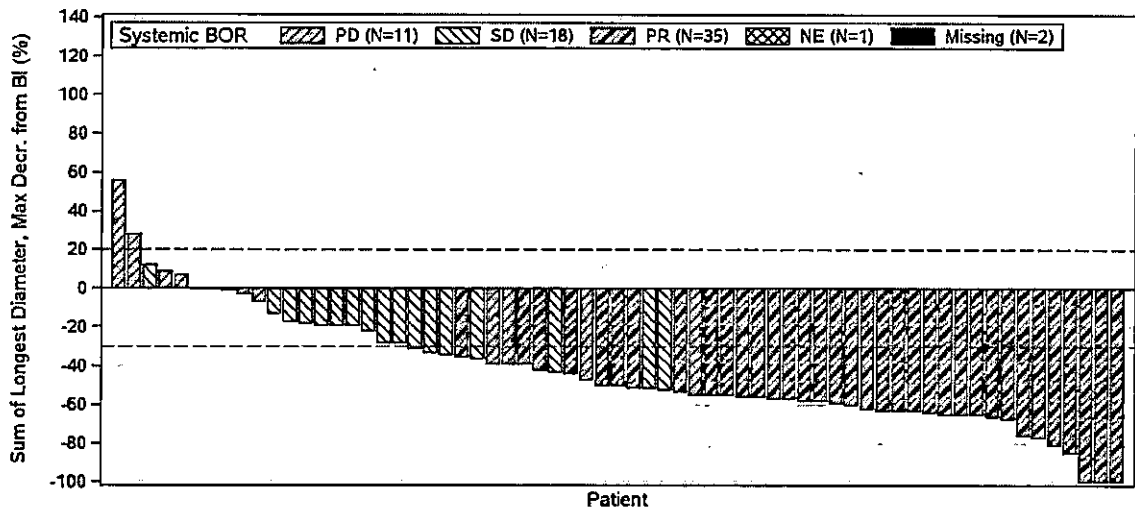
^b Exploratory analysis defined after database lock.

^c DCR calculated including all patients who achieved Best Overall Response (BOR) of SD (minimum duration of 5 weeks as per IRC Charter).

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As shown in the waterfall plot in Figure 4, most patients experienced tumour shrinkage of their defined target lesions, as assessed by the IRC according to RECIST 1.1.

Figure 4 Waterfall plot of target lesions sum of longest diameters best change from baseline shaded by best overall response (IRC) from NP28673 study



BOR= Best overall response, PD = progressive disease, SD = stable disease, PR = partial response, NE = not estimable.

A summary of the pooled analysis of the Central Nervous System (CNS) endpoints based on RECIST (IRC) performed on patients with measurable CNS lesions at baseline (N=50) included in the phase II NP28761 and NP28673 is presented in the below table.

Table 8 Summary of the pooled analysis for CNS endpoints from NP28761 and NP28673 studies

CNS Parameters (NP28761 and NP28673)	Alecensa 600 mg twice daily
Patients with Measurable CNS Lesions at Baseline	N = 50
CNS ORR (IRC)	
Responders (%)	32 (64.0%)
[95% CI]	[49.2%, 77.1%]
Complete Response	11 (22.0%)
Partial Response	21 (42.0%)
CNS DCR (IRC)	
CR+PR+SD ^a	45 (90.0%)

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[95% CI]	[78.2%, 96.7%]
CNS DOR (IRC)	N=32
Number of patients with events (%)	18 (56.3%)
Median (months)	11.1
[95% CI]	[7.6; NE]

CI = confidence interval; CR=complete response; DCR = disease control rate; DOR = duration of response; IRC = independent review committee; NE= not estimable ; ORR = objective response rate; PR = partial response; SD = stable disease

^aDCR calculated including all patients who achieved a Best Overall Response (BOR) of SD (minimum duration of 5 weeks as per IRC Charter).

In 136 patients included in the phase II NP28761 and NP28673 with measurable and/or non-measurable CNS lesions at baseline, the CNS complete response rate was 28.7%. A CNS partial response cannot be established in non-measurable CNS lesions per RECIST. The CNS disease control rate was 86.0% [95% CI (79.1, 91.4)].

3.1.3 Immunogenicity

Not applicable.

3.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic parameters for alectinib and its major active metabolite (M4), have been characterized in ALK-positive NSCLC patients and healthy subjects. The geometric mean (coefficient of variation %) steady-state C_{max} , C_{min} and AUC_{0-12hr} for alectinib were approximately 665 ng/mL (44.3%), 572 ng/mL (47.8 %) and 7430 ng*h/mL (45.7 %), respectively. The geometric mean steady-state C_{max} , C_{min} and AUC_{0-12hr} for M4 were approximately 246 ng/mL (45.4 %), 222 ng/mL (46.6 %) and 2810 ng*h/mL (45.9 %), respectively.

3.2.1 Absorption

Following oral administration of 600 mg twice daily under fed conditions in ALK-positive NSCLC patients, alectinib was rapidly absorbed reaching T_{max} after approximately 4 to 6 hours.

Alectinib steady-state is reached by Day 7 with continuous 600 mg twice daily dosing and remains stable thereafter. The geometric mean accumulation ratio estimated by population PK analysis for the twice-daily 600 mg regimen is 5.6. Population PK analysis supports dose proportionality for alectinib across the dose range of 300 to 900 mg under fed conditions.

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The absolute bioavailability of alectinib was 36.9% (90% CI: 33.9%, 40.3%) under fed conditions in healthy subjects.

Following a single oral administration of 600 mg with a high-fat, high-calorie meal, exposure increased by 3-fold relative to fasted conditions (geometric mean ratio [90% CI] of combined alectinib and M4: C_{max}: 3.31 [2.79 – 3.93], AUC_{inf}: 3.11 [2.73 – 3.55]).

3.2.2 Distribution

Alectinib and its major metabolite M4 are highly bound to human plasma proteins (>99%), independent of drug concentration. The mean *in vitro* human blood-to-plasma concentration ratios of alectinib and M4 are 2.64 and 2.50, respectively, at clinically relevant concentrations.

The geometric mean volume of distribution at steady state (V_{ss}) of alectinib following IV administration was 475 L, indicating extensive distribution into tissues.

3.2.3 Metabolism

In vitro metabolism studies showed that CYP3A4 is the main CYP isozyme mediating alectinib and its major metabolite M4 metabolism, and is estimated to contribute 40-50% of alectinib metabolism in human hepatocytes. Results from the human mass balance study demonstrated that alectinib and M4 were the main circulating moieties in plasma with alectinib and M4 together constituting approximately 76% of the total radioactivity in plasma. The geometric mean Metabolite/Parent ratio at steady state is 0.399.

3.2.4 Elimination

Following administration of a single dose of ¹⁴C-labeled alectinib administered orally to healthy subjects the majority of radioactivity was excreted in feces (mean recovery 97.8%, range 95.6%-100%) with minimal excretion in urine (mean recovery 0.46%, range 0.30%-0.60%). In feces, 84% and 5.8% of the dose was excreted as unchanged alectinib or M4, respectively.

Based on a population PK analysis, the apparent clearance (CL/F) of alectinib was 81.9 L/hour. The geometric mean of the individual elimination half-life estimates for alectinib was 32.5 hours. The corresponding values for M4 were 217 L/hour and 30.7 hours, respectively.

3.2.5 Pharmacokinetics in Special Populations

Pediatric population

No studies have been conducted to investigate the pharmacokinetics of Alecensa in this population.

Geriatric population

Age does not have an effect on Alecensa exposure.

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Renal impairment

Negligible amounts of alectinib and the active metabolite M4 are excreted unchanged in urine (< 0.2 % of the dose). Data obtained in patients with mild and moderate renal impairment show that the pharmacokinetics of alectinib are not significantly affected in renal impairment. No formal pharmacokinetic study has been conducted and no population PK data was collected in patients with severe renal impairment, however since alectinib elimination via the kidney is negligible no dose adjustment is required in renal impairment.

Hepatic impairment

As elimination of alectinib is predominantly through metabolism in the liver, hepatic impairment may increase the plasma concentration of alectinib and/or its major active metabolite M4. Based on a population pharmacokinetic analysis, alectinib and M4 exposures were similar in patients with mild hepatic impairment (baseline total bilirubin less than or equal to ULN and baseline AST greater than ULN or baseline total bilirubin greater than 1.0 to 1.5 times ULN and any baseline AST) and normal hepatic function (total bilirubin less than or equal to ULN and AST less than or equal to ULN).

Following administration of a single oral dose of 300 mg alectinib in subjects with moderate (Child-Pugh B) hepatic impairment the combined exposure of alectinib and M4 was modestly increased compared with matched healthy subjects (geometric mean ratio [90% confidence interval] for moderate/healthy: C_{max} : 1.16 [0.786 – 1.72], AUC_{inf} : 1.36 [0.947 – 1.96]). Administration of a single oral dose of 300 mg alectinib in subjects with severe (Child-Pugh C) hepatic impairment resulted in a greater increase in the combined exposure of alectinib and M4 compared with matched healthy subjects (geometric mean ratio [90% confidence interval] for severe/healthy: C_{max} : 0.981 [0.517 – 1.86], AUC_{inf} : 1.76 [0.984 – 3.15]).

No dose adjustments are required for Alecensa in patients with underlying mild or moderate hepatic impairment. Patients with underlying severe hepatic impairment should receive a dose of 450 mg given orally twice daily (total daily dose of 900 mg).

3.3 NONCLINICAL SAFETY

3.3.1 Carcinogenicity

No carcinogenicity studies have been performed to establish the carcinogenic potential of Alecensa.

3.3.2 Genotoxicity

Alectinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay but induced a slight increase in numerical aberrations in the *in vitro* cytogenetic assay using

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Chinese Hamster Lung (CHL) cells with metabolic activation, and 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.

3.3.3 Impairment of Fertility

No fertility studies in animals have been performed to evaluate the effect of Alecensa. No adverse effects on male and female reproductive organs were observed in general toxicology studies conducted in rats and monkeys at exposures equal to or greater than 2.6 and 0.5 fold, respectively, of the human exposure measured by AUC at the recommended dose of 600 mg twice daily.

3.3.4 Reproductive toxicity

In animal studies, a maternal dose of alectinib equivalent to 2.7-times the recommended human dose of 600 mg twice-daily (based on AUC), caused embryo-fetal loss (miscarriage) in pregnant rabbits. The same equivalent dose given to pregnant rats resulted in small fetuses with retarded ossification and minor abnormalities of the organs.

3.3.5 Other

Alectinib absorbs UV light between 200 and 400 nm and demonstrated phototoxic potential in an *in vitro* photosafety test in cultured murine fibroblasts after UVA irradiation.

Target organs in both rat and monkey at clinically relevant exposures in the repeat-dose toxicology studies included, but were not limited to the erythroid system, gastrointestinal tract and hepatobiliary system.

Abnormal erythrocyte morphology was observed at exposures equal or greater than 10-60% the human exposure by AUC at the recommended dose. Proliferative zone extension in GI mucosa in both species was observed at exposures equal to or greater than 20-120% of the human AUC exposure at the recommended dose. Increased hepatic alkaline phosphatase (ALP) and direct bilirubin as well as vacuolation/degeneration/necrosis of bile duct epithelium and enlargement/focal necrosis of hepatocytes was observed in rats and/or monkeys at exposures equal to or greater than 20-30% of the human exposure by AUC at the recommended dose.

A mild hypotensive effect has been observed in monkeys at around clinically relevant exposures.

Alectinib crossed the blood brain barrier in rats and was retained within brain tissue with a CNS-to-plasma radio-concentration ratio ranging from 0.9 to 1.5 at 24 hrs post-dose.

4. PHARMACEUTICAL PARTICULARS

4.1 STORAGE

Do not store above 30°C.

Keep container tightly closed, protect from light and moisture.

This medicine should not be used after the expiry date (EXP) shown on the pack.

**4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND
DISPOSAL**

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

4.3 PACKS

Capsules 150 mg

224

Medicine: keep out of reach of children

Current in October 2017

Imported by Roche Thailand, Ltd., Bangkok