PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrALECENSARO®

alectinib (as alectinib hydrochloride)

Capsule, 150 mg

Protein Kinase Inhibitor (L01XE)

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Table of Contents

PrALECENSARO®

alectinib (as alectinib hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
oral	Capsule / 150 mg	lactose monohydrate, sodium lauryl sulfate *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

ALECENSARO (alectinib) is indicated:

- for the first-line treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC).

- as monotherapy for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Marketing authorization of ALENCENSARO for the latter indication is primarily based on tumor objective response rate and duration of response; no overall survival benefit has been demonstrated (see CLINICAL TRIALS).

Geriatrics (≥ 65 years of age):
Of the 405 patients in ALECENSARO pivotal clinical trials treated at a dose of 600 mg twice daily, 59 (14.6%) were of age 65 to 74 years and 14 (3.5%) were of age > 75 years. Safety and efficacy of ALECENSARO are generally consistent between older (65 to 74 years of age and ≥ 75 years of age) and younger patients (< 65years of age), although a greater percentage of older patients compared with younger patients experienced adverse events with fatal outcomes, including 6.8% (4/59) for 65 to 74 years of age and 14.3% (2/14) for ≥ 75 years of age vs. 1.8% (6/332) for <65 years of age, or leading to treatment withdrawal (10.2% for 65 to 74 years of age and 28.6% for ≥ 75 years of age vs. 6.6% for <65 years of age).

Pediatrics (<18 years of age):
The safety and efficacy of ALECENSARO in children and adolescents have not yet been established.

CONTRAINDICATIONS

ALECENSARO (alectinib) is contraindicated in:

- Patients with known hypersensitivity to alectinib or any of the excipients. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Gastrointestinal perforation (see WARNINGS AND PRECAUTIONS, Gastrointestinal)
- Interstitial lung disease (see WARNINGS AND PRECAUTIONS, Respiratory)
- Hepatotoxicity (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic)
- Bradycardia (see WARNINGS AND PRECAUTIONS, Cardiovascular)

ALECENSARO has not been studied in patients with severe renal impairment (see WARNINGS AND PRECAUTIONS, Special Populations)

ALECENSARO should be prescribed and supervised by a qualified physician experienced in the use of anticancer agents.

General

Patients treated with ALECENSARO must have a documented ALK-positive status based on a validated ALK assay. Assessment for ALK-positive locally advanced or metastatic NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance can lead to unreliable test results.

Carcinogenesis and Mutagenesis

No carcinogenicity studies have been conducted with ALECENSARO. *In vitro*, alectinib is aneugenic, but not mutagenic or clastogenic (see TOXICOLOGY).

Cardiovascular

Bradycardia

Cases of bradycardia and sinus bradycardia have been reported in patients treated with alectinib in pivotal clinical trials. All of these events were Grade 1 or 2 and generally asymptomatic; none was reported as serious. In two patients, bradycardia/sinus bradycardia led to dose reduction. Treatment was interrupted due to bradycardia and sinus bradycardia in two patients. Symptomatic bradycardia can occur with ALECENSARO (see ADVERSE REACTIONS).

ALECENSARO treatment resulted in a decrease in heart rate (HR) of approximately 11 to 13 bpm at Week 2 in the Phase I/II studies with crizotinib pre-treated patients, which was maintained throughout the treatment period. The decrease in HR was reversible upon

discontinuation. In the Phase III study with treatment-naïve patients, the median decrease in HR reached a plateau of approximately 17 bpm at Week 4. Overall, 20% of patients in the Phase I/II studies and 15% of the patients in the Phase III study displayed lowest post-baseline HRs below 50 bpm. The reduction on HR appears to be correlated to alectinib plasma concentration. Patients presenting with baseline symptomatic bradycardia or QTc interval > 470 millisecond (msec) were not studied in the pivotal clinical trials.

Co-administration of medicines that lower HR should be avoided to the extent possible (see DRUG INTERACTIONS). If avoidance is not possible, patients should be closely monitored.

Heart rate and blood pressure should be monitored at baseline and regularly during treatment (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). Dose modification is not required in case of asymptomatic bradycardia *(*see DOSAGE AND ADMINISTRATION). If patients experience symptomatic bradycardia or life-threatening events, ALECENSARO treatment should be withheld, then reinstituted at a reduced dose or permanently discontinued (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Caution should be exercised in patients with a low heart rate at baseline (< 60 bpm), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, or congestive heart failure. Cardiology consultation may be required.

Patients should be informed that symptoms of bradycardia including dizziness, lightheadedness, and syncope can occur while taking ALECENSARO. Advise patients to contact their healthcare provider to report these symptoms and to inform their healthcare provider about the use of any heart or blood pressure medications.

Gastrointestinal

Gastrointestinal perforation
Across all pivotal clinical trials, one case of gastrointestinal perforation (0.2%) occurred and had a fatal outcome. In the post-market setting cases of gastrointestinal perforation were also reported with ALECENSARO.

In patients at risk for gastrointestinal perforation (e.g. concomitant use of medications with a risk of gastrointestinal perforation, history of diverticulitis, metastases to the gastrointestinal tract) ALECENSARO should be used with caution. Patients should be informed of potential signs of gastrointestinal perforations and seek consultation rapidly in case of occurrence.

Discontinue ALECENSARO permanently in patients who develop gastrointestinal perforation (see DOSAGE AND ADMINISTRATION).

Hepatic/Biliary/Pancreatic

Hepatoxicity
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 clinical trials with ALECENSARO (see ADVERSE REACTIONS).

The majority of these events occurred during the first 3 months of treatment (69% of the patients with hepatic transaminase elevations and 64% of the patients with bilirubin elevations in the pivotal studies including 405 patients). In the pivotal clinical trials, two patients with Grade 3-4 AST/ALT elevations had documented drug induced liver injury by liver biopsy. In addition, one patient experienced a Grade 4 adverse event of drug-induced liver injury and another patient experienced Grade 4 hepatotoxicity. 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 less than 1% of the patients treated in ALECENSARO 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 during treatment, 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, ALECENSARO may need to be withheld, resumed at a reduced dose, or permanently discontinued (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Musculoskeletal

Severe Myalgia and Creatine Phosphokinase (CPK) elevation
Myalgia and musculoskeletal pain were reported in patients in pivotal trials with ALECENSARO, including events of Grade 3 intensity (see ADVERSE REACTIONS).

Elevations of CPK occurred in pivotal trials with ALECENSARO, including events of Grade 3 intensity. Median time to Grade 3 CPK elevation was 15 days in the pivotal clinical trials (see ADVERSE REACTIONS).

Patients should be advised to report any unexplained muscle pain, tenderness, or weakness. CPK levels should be assessed 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, ALECENSARO may need to be withheld or resumed at a reduced dose (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Renal

Renal Impairment
Renal impairment was reported in the pivotal clinical trials with ALECENSARO (see ADVERSE REACTIONS) with grades above or equal to 3. Based on the severity of the renal impairment, ALECENSARO may need to be withheld, resumed at a reduced dose, or permanently discontinued (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Respiratory

Interstitial Lung Disease (ILD) / Pneumonitis

Cases of ILD/pneumonitis have been reported in clinical trials with ALECENSARO (see ADVERSE REACTIONS). Patients should be monitored for pulmonary symptoms indicative of pneumonitis. ALECENSARO 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 DOSAGE AND ADMINISTRATION).

Sexual Function/Reproduction

Fertility
The effect of ALECENSARO on fertility is unknown (see TOXICOLOGY).

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

Skin

Photosensitivity
Photosensitivity to sunlight has been reported with ALECENSARO administration (see ADVERSE REACTIONS). Patients should be advised to avoid prolonged sun exposure while taking ALECENSARO 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.

Special Populations

Pregnant Women*:* No clinical studies of ALECENSARO in pregnant women have been performed. Based on its mechanism of action, ALECENSARO may cause fetal harm when administered to pregnant women. In animal studies, alectinib caused embryo-fetal toxicity and abortion.

Women of childbearing potential must be advised to avoid pregnancy while on ALECENSARO. Female patients of child-bearing potential must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of ALECENSARO.
Female patients who become pregnant while taking ALECENSARO or during the 3 months following the last dose of ALECENSARO must contact their doctor and should be advised of the potential harm to the fetus.

Nursing Women*:* It is not known whether ALECENSARO is excreted in human breast milk. No studies have been conducted to assess the impact of ALECENSARO 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 ALECENSARO.

Males: Adequate contraceptive methods should be used by male patients during therapy, and for at least 3 months after completing therapy. If the patient's partner becomes pregnant while receiving ALECENSARO, then the patient and his partner should be advised of the potential harm to the fetus.

Geriatrics (≥ 65 years of age):
Of the 405 patients in ALECENSARO pivotal clinical trials treated at a dose of 600 mg twice daily, 59 (14.6%) were of age 65 to 74 years and 14 (3.5%) were of age ≥75 years. Severe (Grade 3-5) adverse events (AEs) were reported in 39.5% of the patients aged < 65 years, in 39.0% of the patients aged 65 to 74 years, and in 64.3% of the patients aged ≥ 75 years. Serious AEs were reported in 22.9% of the patients aged < 65 years, in 27.1% of the patients aged 65 to 74 years, and in 42.9% of the patients aged ≥ 75 years. AEs with fatal outcome occurred in 1.8% of the patients aged < 65 years, in 6.8% of the patients aged 65 to 74 years, and in 14.3% of the patients aged ≥ 75 years. AEs led to treatment withdrawal in 6.6% of the patients aged < 65 years, in 10.2% of the patients aged 65 to 74 years, and in 28.6% of the patients aged ≥ 75 years.

Pediatrics (<18 years of age): The safety and efficacy of ALECENSARO in children and adolescents have not been established.

Decreased bone formation and lesions in the continuously growing incisor teeth were observed in young rats given 27 mg/kg/day following once daily dosing for 13 weeks at which systemic exposure to alectinib was 2.4 and 2.8 times that at the adult human dose, in male and female rats, respectively. These findings may indicate a potential risk to growing bones and teeth in pediatric patients.

Renal Impairment: No dose adjustment is required in patients with mild or moderate renal impairment (CrCl 30 to less than 90 mL/min). ALECENSARO has not been studied in patients with severe renal impairment (CrCl less than 30 mL/min). (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

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 DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment). For all patients with hepatic impairment, appropriate monitoring (e.g. markers of liver function) is advised (see WARNINGS AND PRECAUTIONS, Hepatotoxicity). In the alectinib pivotal trials, only patients with adequate hepatic function have been included (ALT and AST ≤2.5x ULN or ≤5x ULN for patients with liver metastases at baseline, and bilirubin ≤2mg/dL) (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions).

Monitoring and Laboratory Tests

ALK testing

Patients treated with ALECENSARO must have a documented ALK-positive status based on a validated ALK assay. Assessment for ALK-positive locally advanced or metastatic NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance can lead to unreliable test results.

Cardiac Safety Monitoring
Heart rate and blood pressure should be monitored at baseline and regularly during treatment. Serum calcium and potassium should be monitored periodically during treatment. Patients should be informed that symptoms of bradycardia including dizziness, lightheadedness, and syncope can occur while taking ALECENSARO. Advise patients to contact their healthcare provider to report these symptoms and to inform their healthcare provider about the use of any heart or blood pressure medications. Dose modification is not required in case of asymptomatic bradycardia (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment). If patients experience symptomatic bradycardia or life-threatening events, ALECENSARO treatment should be withheld, then reinstituted at a reduced dose or permanently discontinued. ALECENSARO should be permanently discontinued in case of recurrence of severe, life-threatening bradycardia or in case of life-threatening bradycardia if no contributing medication is identified (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Liver Function Monitoring
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 ALECENSARO and resume at a reduced dose, or permanently discontinue ALECENSARO (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Blood CPK Monitoring
Patients should be advised to report any unexplained muscle pain, tenderness, or weakness. CPK levels should be assessed 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, ALECENSARO should be withheld, then resumed or dose should be reduced (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Crizotinib pre-treated patients
The most common adverse drug reactions (≥10%) in clinical trials were: fatigue, constipation, edema, myalgia, nausea, headache, rash, diarrhea, increased bilirubin, aspartate aminotransferase increased, anemia, alanine aminotransferase increased, vomiting, blood creatine phosphokinase increased, weight increased, vision disorders, dizziness, photosensitivity reaction and arthralgia.

In the pivotal phase I/II clinical trials, serious adverse reactions were reported in 22% of the patients and the most frequently reported serious adverse reactions were pulmonary embolisms, dyspnea and hyperbilirubinemia (1.2% each). Fatal adverse reactions in patients treated with ALECENSARO occurred in 2.8% of patients, consisting of hemorrhage (2 patients, 0.8%), intestinal perforation, dyspnea, pulmonary embolism, endocarditis and death (unspecified) (1 patient each, 0.4%).

In the pivotal phase I/II clinical trials, permanent discontinuation of therapy due to adverse reactions occurred in 6% of patients treated with ALECENSARO. The most frequent adverse reactions that led to permanent discontinuation were increased bilirubin (1.6%, including blood bilirubin increased, hyperbilirubinemia and bilirubin conjugated increased), increased ALT levels (1.6%) and increased AST levels (1.2%). Dose reductions due to adverse reactions occurred in 13% of patients treated with ALECENSARO and dose interruptions occurred in 29%. The most frequent adverse reactions that led to dose reductions or interruptions were elevations in bilirubin (6%), elevations in ALT and creatine phosphokinase (CPK) (4% each) as well as AST elevations and vomiting (3% each).

Treatment-naïve patients

The most common adverse drug reactions for ALECENSARO (≥10%) in the pivotal phase III trial were: constipation, myalgia, fatigue, edema, increased bilirubin, anemia, rash, alanine aminotransferase increased, aspartate aminotransferase increased, nausea, diarrhea, arthralgia and bradycardia.

In the pivotal phase III clinical trial, serious adverse reactions occurred in 28% of patients treated with ALECENSARO; the most frequently reported serious adverse reactions were pneumonia (3.3%) and acute kidney injury (2.6%). Grade ≥3 adverse events were reported for 41% of patients in the ALECENSARO arm. Fatal adverse reactions occurred in 5 patients (3.3%) in the ALECENSARO arm.

In the pivotal phase III clinical trial, permanent treatment discontinuation for adverse reactions occurred in 11% of patients treated with ALECENSARO. Acute kidney injury was the most commonly reported adverse drug reaction leading to study drug discontinuation (2.0%). Dose modifications (dose reductions and drug interruption, respectively) were required in 16% and 19% of patients in the ALECENSARO arm. The most frequent adverse reactions that led to dose modifications in the ALECENSARO arm were pneumonia, elevation in ALT and AST.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse

events and for approximating rates.

Crizotinib pre-treated patients

The safety of ALECENSARO has been evaluated in 253 patients in the pivotal Phase I/II (NP28761, NP28673) clinical trials 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 ALECENSARO was 11 months (range 0-35 months).

Per the pivotal phase I/II clinical study protocols, eligible patients should have adequate hematological, renal and hepatic functions and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Patients with NCI CTCAE Grade 3 or higher toxicities due to prior therapy that had not shown improvement were excluded. All but one patient have progressed on previous treatment with crizotinib.

Table 1 summarizes the adverse reactions (ARs) occurring in ≥2% patients who received ALECENSARO in the pivotal Phase I/II clinical trials (NP28761 and NP28673).

Table 1 Summary of Adverse Reactions Occurring in ≥2% Patients Treated with ALECENSARO in the pivotal Phase I/II Clinical Trials (NP28761 and NP28673)

Adverse Reactions (MedDRA)	**ALECENSARO N=253 (NP28761, NP28673)**	
System Organ Class	**All Grades n (%)**	**Grade 3 – 4* n (%)**
Blood and Lymphatic System Disorders		
Anemia[1]	40 (16)	5 (2.0)
Neutropenia	9 (3.6)	1 (0.4)
Leukopenia	9 (3.6)	0
Cardiac Disorders		
Bradycardia[2]	20 (7.9)	0
Eye Disorders		
Vision Disorders[3]	29 (12)	0
Gastrointestinal Disorders		
Constipation	90 (36)	0
Nausea	55 (22)	1 (0.4)
Diarrhea	46 (18)	3 (1.2)
Vomiting	34 (13)	1 (0.4)
Stomatitis[4]	7 (2.8)	0
General Disorders and Administration Site Conditions		
Fatigue[5]	112 (44)	4 (1.6)
Edema[6]	85 (34)	2 (0.8)
Mucosal Inflammation	7 (3)	0
Investigations		

Increased Bilirubin[7]	42 (17)	8 (3.2)
Aspartate Aminotransferase Increased	41 (16)	7 (2.8)
Alanine Aminotransferase Increased	35 (14)	8 (3.2)
Blood Creatine Phosphokinase Increased	34 (13)	9 (3.6)
Weight Increased	34 (13)	2 (0.8)
Blood Alkaline Phosphatase Increased	19 (7.5)	1 (0.4)
Blood Creatinine Increased	17 (6.7)	1 (0.4)
Musculoskeletal and Connective Tissue Disorders		
Myalgia[8]	78 (31)	3 (1.2)
Arthralgia	28 (11)	0
Muscular Weakness	17 (6.7)	1 (0.4)
Nervous System Disorders		
Headache	50 (20)	3 (1.2)
Dizziness	29 (12)	0
Dysgeusia	16 (6.3)	0
Neuropathy peripheral	11 (4.3)	0
Skin and Subcutaneous Tissue Disorders		
Rash[9]	51 (20)	1 (0.4)
Photosensitivity Reaction	29 (12)	0
Dry Skin	17 (6.7)	0
Alopecia	13 (5.1)	0
Pruritus	11 (4.3)	0

[*] no Grade 5 events observed
[1] includes cases of anemia and haemoglobin decreased
[2] includes cases of bradycardia and sinus bradycardia
[3] includes cases of vision blurred, visual impairment, vitreous floaters, visual acuity reduced, asthenopia, and diplopia
[4] includes cases of stomatitis and mouth ulceration
[5] includes cases of fatigue and asthenia
[6] includes cases of edema peripheral, edema, generalised edema, eyelid edema, periorbital edema
[7] includes cases of blood bilirubin increased, hyperbilirubinemia and bilirubin conjugated increased
[8] includes cases of myalgia and musculoskeletal pain
[9] includes cases of rash, rash maculopapular, dermatitis acneiform, erythema, rash generalized, rash papular, rash pruritic and rash macular

Less Common Severe or Serious Clinical Trial Adverse Drug Reactions (<2%)

Hepatic: Drug-induced liver injury (0.8%) (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).
Respiratory: Interstitial lung disease (0.4%)
Gastrointestinal: Gastrointestinal perforation (0.4%).

Additional safety information from clinical trial experience

Abnormal ECG findings
Cases of bradycardia (7.9%) have been reported in patients treated with ALECENSARO in pivotal Phase I/II clinical trials; all cases were of Grade 1 or 2 intensity. There were 44 of 221 patients (20%) treated with ALECENSARO who had post-dose heart rate values below 50 bpm.

One patient experienced treatment-related Grade 1, non-serious QTcF prolongation (< 500 millisecond [msec]). In addition, one patient had an absolute QTcF value > 500 msec and one patient had a change from baseline in QTcF > 60 msec (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

Interstitial Lung Disease (ILD)/pneumonitis

Severe ILD/pneumonitis has occurred in patients treated with ALECENSARO. In the pivotal Phase I/II clinical trials, 1 out of 253 patients treated with ALECENSARO (0.4%) had a Grade 3 ILD leading to withdrawal from ALECENSARO treatment. There were no fatal cases of ILD in any of the clinical trials.

Hepatotoxicity

In the pivotal Phase I/II trials, three patients with Grade 3-4 AST/ALT elevations had drug induced liver injury (DILI) by liver biopsy. Adverse reactions of increased AST and ALT levels (16% and 14% respectively) were reported in patients treated with ALECENSARO in pivotal Phase I/II clinical trials. The majority of these events were of Grades 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 ALECENSARO 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 ALECENSARO treatment.

Adverse reactions of bilirubin elevations were reported in 17% of the patients treated with ALECENSARO in pivotal Phase I/II clinical trials. 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 ALECENSARO treatment (4.7 % of the patients) or dose reduction (2.8%). In 4 patients (1.6%), bilirubin elevations led to withdrawal from ALECENSARO treatment.

Concurrent elevations in ALT or AST greater than or equal to 3 times the ULN and total bilirubin greater than or equal to 2 times the ULN, with normal alkaline phosphatase, occurred in less than 1% of the patients treated with ALECENSARO.

Severe Myalgia

Cases of myalgia (31%) including myalgia events (25%) and musculoskeletal pain (7.5%) have been reported in patients treated with ALECENSARO in pivotal phase I/II clinical trials. The majority of events were Grade 1 or 2, and 1.2% of the patients had a Grade 3 event. Dose modifications of ALECENSARO treatment due to these adverse events were required for two patients (0.8%).

CPK elevation

Elevations of CPK occurred in 46% of 219 patients with CPK laboratory data available in pivotal phase II clinical trials with ALECENSARO. The incidence of Grade 3 elevations of CPK was 4.0%. Median time to Grade 3 CPK elevation was 14 days in the pivotal phase I/II trials. Dose modifications for elevation of CPK occurred in 4.0% of patients.

Abnormal Hematologic and Clinical Chemistry Findings

Table 2 displays treatment-emergent shifts in laboratory abnormalities occurring in patients treated with ALECENSARO.

Table 2 Treatment-Emergent Laboratory Abnormalities Occurring in ≥ 20% Patients Treated with ALECENSARO in Phase I/II NP28761 and NP28673 Clinical Trials

Parameter	**Alectinib N= 250***	
	All Grade %	**Grade 3 – 4 %**
Chemistry		
Increased AST	53	3.6
Increased Alkaline Phosphatase	50	1.2
Increased Blood Creatine Phosphokinase	46	5.0
Increased Bilirubin (total)	42	3.2
Hyperglycemia	40	2.0
Increased ALT	36	4.8
Hypocalcemia	35	0.4
Increased Blood Creatinine**	31	0
Hypokalemia	31	4.4
Hyponatremia	25	2.0
Hypophosphatemia	23	3.2
Hematology		
Decreased Hemoglobin	60	2.0
Lymphopenia	25	6.0

Data comprise all laboratory test shifting of at least one NCI CTC AE grade higher compared to baseline, regardless of causality.
AST - Aspartate Aminotransferase, ALT - Alanine Aminotransferase
* N= 219 for Creatine Phosphokinase, N=152 for fasting blood glucose, N=218 for lymphocytes
** Only patients with creatinine increases based on ULN definition (CTC AE grading)

Treatment-naïve patients

The safety of ALECENSARO 600 mg twice daily compared to crizotinib 250 mg twice daily was evaluated in 152 and 151 patients with ALK-positive NSCLC, respectively, in the pivotal Phase III clinical trial (BO28984). The median duration of exposure to ALECENSARO and crizotinib was 17.9 and 10.7 months, respectively. Baseline demographics and disease characteristics for ALECENSARO patients 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).

The trial was a randomized, multicenter, open-label study. Patients were treated until disease progression, unacceptable toxicity, withdrawal of consent, or death, whichever occurred first. Per the pivotal phase III clinical trial protocol, randomized patients had adequate hematological, hepatic, and renal function and an ECOG performance status of 0 to 2 at baseline.

Table 3 summarizes the adverse reactions (ARs) occurring in ≥2% patients who received either ALECENSARO or crizotinib in the pivotal Phase III clinical trial BO28984.

Table 3 Summary of Adverse Reactions Occurring in ≥2% Patients Treated with ALECENSARO or crizotinib in the pivotal Phase III clinical trial BO28984

Adverse Reactions (MedDRA)	**Alecensaro N=152**		**Crizotinib N=151**	
System Organ Class	**All Grades n (%)**	**Grades 3–4 n (%)**	**All Grades n (%)**	**Grades 3–4 n (%)**
Blood and Lymphatic System Disorders				
Anemia[1]	30 (19.7)	7 (4.6)	7 (4.6)	1 (0.7)
Cardiac Disorders				
Bradycardia[2]	16 (10.5)	0	22 (14.6)	0
Eye Disorders				
Vision disorders[3]	7 (4.6)	0	35 (23.2)	0
Gastrointestinal Disorders				
Constipation	52 (34.2)	0	49 (32.5)	0
Nausea	21 (13.8)	1 (0.7)	72 (47.7)	5 (3.3)
Diarrhea	18 (11.8)	0	68 (45.0)	3 (2.0)
Vomiting	11 (7.2)	0	58 (38.4)	5 (3.3)
Stomatitis[4]	5 (3.3)	0	4 (2.6)	0
General Disorders and Administration Site Conditions				

Adverse Reactions (MedDRA)	**Alecensaro N=152**		**Crizotinib N=151**	
System Organ Class	**All Grades n (%)**	**Grades 3–4 n (%)**	**All Grades n (%)**	**Grades 3–4 n (%)**
Fatigue[5]	39 (25.7)	2 (1.3)	34 (22.5)	1 (0.7)
Edema[6]	34 (22.4)	1 (0.7)	51 (33.8)	1 (0.7)
Investigations				
Increased Bilirubin[7]	32 (21.1)	5 (3.3)	2 (1.3)	0
Alanine Aminotransferase Increased	23 (15.1)	7 (4.6)	45 (29.8)	22 (14.6)
Aspartate Aminotransferase Increased	21 (13.8)	8 (5.3)	37 (24.5)	16 (10.6)
Weight increased	15 (9.9)	1 (0.7)	0	0
Blood Creatinine Increased	12 (7.9)	2 (1.3)	6 (4.0)	1 (0.7)
Blood Creatine Phosphokinase Increased	8 (5.3)	4 (2.6)	7 (4.6)	2 (1.3)
Musculoskeletal and Connective Tissue Disorders				
Myalgia[8]	35 (23.0)	0	6 (4.0)	0
Arthralgia	17 (11.2)	0	11 (7.3)	2 (1.3)
Nervous System Disorders				

Adverse Reactions (MedDRA)	Alecensaro N=152		Crizotinib N=151	
System Organ Class	**All Grades n (%)**	**Grades 3–4 n (%)**	**All Grades n (%)**	**Grades 3–4 n (%)**
Dizziness	12 (7.9)	0	21 (13.9)	0
Dysgeusia[9]	5 (3.3)	1 (0.7)	29 (19.2)	0
Renal and Urinary Disorders				
Acute kidney injury	4 (2.6)	4 (2.6*)	0	0
Skin and Subcutaneous Tissue Disorders				
Rash[10]	23 (15.1)	1 (0.7)	19 (12.6)	0
Photosensitivity Reaction	8 (5.3)	1 (0.7)	0	0
Pruritus	5 (3.3)	0	2 (1.3)	0
Dry skin	6 (3.9)	0	1 (0.7)	0

Adverse reactions are reported according to Medical Dictionary for Regulatory Activities (MedDRA, version 19.1).

The intensity of the adverse reactions are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.0);

[1] Includes cases of anemia and hemoglobin decreased.

[2] Includes cases of bradycardia and sinus bradycardia.

[3] Includes cases of blurred vision, visual impairment, vitreous floaters, reduced visual acuity, and diplopia.

[4] Includes cases of stomatitis and mouth ulceration

[5] Includes cases of fatigue and asthenia

[6] Includes cases of peripheral edema, edema, eyelid edema, localized edema, and face edema.

[7] Includes cases of increased blood bilirubin, hyperbilirubinemia and increased bilirubin conjugated.

[8] Includes cases of myalgia and musculoskeletal pain.

[9] Includes cases of dysgeusia and hypogeusia.

[10] Includes cases of rash, rash maculo-papular, dermatitis acneiform, erythema, generalized rash, rash macular, rash papular, exfoliative rash, and pruritic rash.

* Includes one Grade 5 event.

Less Common Severe or Serious Clinical Trial Adverse Drug Reactions (<2%)

Hepatobiliary Disorders: Hepatotoxicity (includes cases of drug-induced liver injury and hepatotoxicity).
Respiratory, Thoracic and Mediastinal Disorders: Interstitial Lung Disease (includes cases of pneumonitis).

Additional safety information from clinical trial experience

Abnormal ECG findings
Cases of bradycardia (11%) have been reported in patients treated with ALECENSARO in the pivotal Phase III clinical trial; all cases were of Grade 1 or 2 intensity. Out of 144 patients in the

evaluable ECG population treated with ALECENSARO, there were 22 (15%) patients who had post-dose heart rate values below 50 bpm. There was one patient who had a change from baseline in QTcF > 60 msec; none of the patients had a QTcF value > 500 msec (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

Interstitial Lung Disease (ILD)/pneumonitis

Severe ILD/pneumonitis has occurred in patients treated with ALECENSARO. In the pivotal Phase III clinical trial, all cases of ILD/pneumonitis in patients treated with ALECENSARO were of Grade 1 or 2 intensity. There were no fatal cases of ILD in patients treated with ALECENSARO the phase III trial.

Hepatotoxicity

In the pivotal Phase III trial, two patients with Grade 3-4 AST/ALT elevations had hepatotoxicity (including one case of Grade 4 DILI and one case of Grade 4 hepatotoxicity). Laboratory abnormalities of increased AST and ALT levels were reported as adverse reactions in 14% and 15%, respectively, of the patients treated with ALECENSARO in the pivotal Phase III clinical trial. The majority of these events were of Grades 1 and 2 intensity, and events of Grade ≥ 3 were reported in 5.3% and 4.6% of the patients, respectively. The events generally occurred during the first 3 months of treatment, were usually transient and resolved upon temporary interruption of ALECENSARO treatment (reported for 2.0% and 2.6% of the patients, respectively) or dose reduction (3.3% and 2.0%, respectively). In 1.3% and 1.3% of the patients, AST and ALT elevations, respectively, led to withdrawal from ALECENSARO treatment.

Laboratory abnormalities of increased bilirubin were reported as adverse reactions in 21% of the patients treated with ALECENSARO in the pivotal Phase III clinical trial. The majority of the events were of Grade 1 and 2 intensity; Grade 3 and/or Grade 4 events were reported in 3.3% of the patients. The events generally occurred during the first 3 months of treatment, were usually transient and resolved upon temporary interruption of ALECENSARO treatment or dose reduction. In 2 patients (1.3%), bilirubin elevations led to withdrawal from ALECENSARO treatment.

Severe Myalgia

Cases of myalgia (16%) and musculoskeletal pain (7.2%) have been reported in patients treated with ALECENSARO in the pivotal phase III clinical trial. All the events were of Grade 1 or 2 intensity. No dose modifications or withdrawal of ALECENSARO treatment due to these adverse events were required.

CPK elevation

Elevations of CPK occurred in 37% of 129 patients with CPK laboratory data available in the pivotal phase III clinical trial with ALECENSARO. The incidence of Grade 3 elevations of CPK was 3.1%. Median time to Grade 3 CPK elevation was 27.5 days. Dose modifications for elevation of CPK occurred in 2 patients.

Abnormal Hematologic and Clinical Chemistry Findings

Table 4 displays treatment-emergent shifts in laboratory abnormalities occurring in patients who received either ALECENSARO or crizotinib in the Phase III BO28984 Clinical Trial.

Table 4 Treatment-Emergent Laboratory Abnormalities Occurring in ≥ 20% Patients Treated with ALECENSARO or crizotinib in the Phase III BO28984 Clinical Trial

Parameter	Alecensaro N= 152		Crizotinib N=151	
	All Grades (%)	Grade 3–4 (%)	All Grades (%)	Grade 3–4 (%)
Chemistry				
Increased blood bilirubin	53[b]	5.5[b]	4.7[f]	0
Increased AST	50[c]	6.2[c]	56[f]	11[f]
Increased alkaline phosphatase	50[d]	0	44[f]	0
Increased ALT	40[d]	6.1[d]	62[f]	16[f]
Increased blood creatinine[a]	38[d]	3.4[d]	23[f]	0.7[f]
Increased CPK	37[e]	3.1[e]	51[g]	1.5[g]
Decreased sodium	18[d]	6.1[d]	20[d]	4.1[d]
Hematology				
Decreased Hemoglobin	62[d]	6.8[d]	36[f]	0.7[f]

Note: Laboratory abnormalities were based on the normal ranges of the National Cancer Institute Common Terminology Criteria for Adverse Events v. 4.0.
[a] Only patients with creatinine increases based on ULN definition.
Patients with missing baseline and/or no post-baseline lab assessments were excluded from analyses: b; N=146, c; N=145, d; N=147, e; N=129, f; N=148, g; N=130

Post-Market Adverse Drug Reactions

Serious adverse drug reactions reported in the post-market setting, but not in ALECENSARO clinical trials are as follows:

Cardiac disorders: atrioventricular block complete

Respiratory, Thoracic and Mediastinal Disorders: eosinophilic pneumonia

DRUG INTERACTIONS

Drug-Drug Interactions

Effects of other drugs on ALECENSARO

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 total

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

CYP3A inducers

In a drug interaction study in healthy volunteers (N=24), 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 reduced alectinib exposure (geometric mean ratio with/without rifampicin [90% confidence interval] C_{max}: 0.49 [0.44 , 0.54], AUC_{inf}: 0.27 [0.24 , 0.30]), increased M4 exposure (geometric mean ratio with/without rifampicin [90% confidence interval] C_{max}: 2.20 [1.90 , 2.55], AUC_{inf}: 1.79 [1.58 , 2.02]) and 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]). ALECENSARO and strong CYP3A inducers should be co-administered with caution and patients should be monitored.

CYP3A inhibitors

In a drug interaction study in healthy volunteers (N=17), 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 increased alectinib exposure (geometric mean ratio with/without posaconazole [90% confidence interval] C_{max}: 1.18 [1.02 , 1.37], AUC_{inf}: 1.75 [1.57 , 1.95]), reduced M4 exposure (geometric mean ratio with/without posaconazole [90% confidence interval] C_{max}: 0.29 [0.23 , 0.36], AUC_{inf}: 0.75 [0.64 , 0.88]), and 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]). In the pivotal studies, co-administration of a strong CYP3A inhibitor with ALECENSARO was not permitted; safety evidence is thus limited. If ALECENSARO is co-administered with a strong CYP3A inhibitor, caution should be exercised and patients should be monitored.

Medicinal products that increase gastric pH

Although the aqueous solubility of alectinib in vitro is pH dependent, in a dedicated study in healthy volunteers (N=24), co-administration of multiple oral doses of with 40 mg esomeprazole, a proton pump inhibitor, once daily for 5 days, with a single oral dose of 600 mg alectinib demonstrated no clinically relevant effect on alectinib exposure (geometric mean ratio with/without esomeprazole [90% confidence interval] C_{max}: 1.16 [1.03, 1.32], AUC_{inf}: 1.22 [1.09 , 1.36]), M4 exposure (geometric mean ratio with/without esomeprazole [90% confidence interval] C_{max}: 1.02 [0.870, 1.19], AUC_{inf}: 1.10 [0.963, 1.26]), or the combined exposure of alectinib and M4 (geometric mean ratio with/without esomeprazole [90% confidence interval] C_{max}: 1.13 [1.00, 1.28], AUC_{inf}: 1.17 [1.04, 1.31]). Therefore, no dose adjustments are required when ALECENSARO 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.

Effects of ALECENSARO on other 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.

In vitro studies indicate that alectinib is an inhibitor of CYP2C8. Alectinib may increase plasma concentrations of co-administered CYP2C8 substrates. Alectinib and CYP2C8 substrates should be co-administered with caution and patients should be monitored.

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. When alectinib is co-administered with P-gp or BCRP substrates with narrow therapeutic index (e.g. digoxin, dabigatran, methotrexate), appropriate monitoring is recommended.

Drugs that Decrease Heart Rate and/or Prolong the PR Interval

ALECENSARO results in a decrease in heart rate (see WARNINGS AND PRECAUTIONS; ADVERSE REACTIONS; ACTION AND CLINICAL PHARMACOLOGY). The concomitant use of ALECENSARO with other drugs that lower heart rate, including, but not limited to, beta-adrenoceptor antagonists, alpha2-adrenoceptor agonists, non-dihydropyridine calcium channel blockers, digitalis glycosides, cholinesterase inhibitors, and sphingosine-1 phosphate receptor modulators should be avoided to the extent possible. If avoidance is not possible, patient should be monitored; cardiology consultation may be required.

Drug-Food Interactions

The bioavailability of alectinib is increased in the presence of food. A food effect study conducted in healthy volunteers with a single 600 mg alectinib dose showed that a high-calorie, high-fat meal (containing approximately 900 calories and 57 grams of fat) increased alectinib AUC_{inf} by 2.92-fold and C_{max} by 2.7-fold as compared with the fasted state. (see ACTION AND CLINICAL PHARMACOLOGY). ALECENSARO should be taken with food (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Grapefruit has CYP3A4 inhibitory activity. Therefore, ingestion of grapefruit while on ALECENSARO (alectinib) therapy may increase alectinib plasma concentrations and decrease M4 plasma concentrations. Concomitant administration of ALECENSARO with grapefruit, grapefruit juice, products containing grapefruit extract, star fruit, pomegranate, Seville oranges, and other similar fruits that are known to inhibit CYP3A4 should be done with caution (see DRUG INTERACTIONS, Effects of other drugs on ALECENSARO).

Drug-Herb Interactions

St. John's wort is a strong CYP3A4 inducer. Co-administration with ALECENSARO may decrease alectinib plasma concentrations and increase M4 plasma concentrations. Concomitant administration of ALECENSARO with St. John's wort should be done with caution (see DRUG INTERACTIONS, Effects of other drugs on ALECENSARO).

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Vision disorders, asthenia, fatigue and dizziness have been reported in patients receiving ALECENSARO treatment. Patients experiencing these symptoms should use caution when driving or operating machines.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Standard Dosage

The recommended dose of ALECENSARO is 600 mg (four 150 mg capsules) given orally, twice daily with food (total daily dose of 1200 mg).

Duration of treatment

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

Dose Modification Recommendations

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

Table 5 below presents general dose modification recommendation for ALECENSARO.

Table 5 Dose Reduction Schedule

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

Recommendations for dose modifications of ALECENSARO in case of adverse reactions are provided in Table 6.

Table 6 Dose Modifications for Specific Adverse Drug Reactions

Criteria	ALECENSARO Dosing
Gastrointestinal perforation	Permanently discontinue ALECENSARO.
Interstitial lung disease (ILD)/pneumonitis of any severity grade	Immediately interrupt ALECENSARO treatment and permanently discontinue if no other potential causes of ILD/pneumonitis have been identified.
Renal impairment Grade 3	Temporarily withhold until serum creatinine recovers to baseline or ≤ Grade 1, then resume at reduced dose.
Renal impairment Grade 4	Permanently discontinue ALECENSARO.
ALT or AST elevation of Grade ≥3 (> 5 times ULN) with total bilirubin ≤ 2 times ULN	Temporarily withhold until recovery to baseline or ≤ Grade 1, then resume at reduced dose (see Table 5).
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 ALECENSARO.
Bradycardia[a] Grade 2 or Grade 3 (symptomatic, may be severe and medically significant, medical intervention indicated)	Temporarily withhold until recovery to ≤ 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 ALECENSARO at previous dose upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. If no contributing concomitant medication is

Criteria	ALECENSARO Dosing
	identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose (see Table 5) upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm.
Bradycardia[a] Grade 4 (life-threatening consequences, urgent intervention indicated)	Permanently discontinue ALECENSARO treatment if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at reduced dose (see Table 5) upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 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 ≤ 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 ≤ 2.5 times ULN, then resume at reduced dose as per Table 5.

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

Elderly: No dose adjustment of ALECENSARO is required in patients ≥ 65 years of age.

Renal Impairment: No dose adjustment is required in patients with mild or moderate renal impairment. ALECENSARO has not been studied in patients with severe renal impairment. *(*see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions*).*

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). For all patients with hepatic impairment, appropriate monitoring (e.g. markers of liver function) is advised (see WARNINGS AND PRECAUTIONS, Hepatotoxicity). No dose adjustment is required in patients with underlying mild or moderate hepatic impairment. *(*see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions*).*

Missed Dose

If a dose of ALECENSARO is missed, take the next dose at the next scheduled time.

Vomiting

If vomiting occurs after taking a dose of ALECENSARO, patients should take the next dose at the scheduled time.

OVERDOSAGE

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 ALECENSARO.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Alectinib is a highly selective and potent ALK and RET (Rearranged during Transfection) tyrosine kinase inhibitor. Alectinib inhibited ALK phosphorylation and ALK-mediated downstream signalling pathways including STAT 3 and PI3K/AKT and induces tumour 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.

Alectinib is not a substrate of effux transporters p-glycoprotein (P-gp) or Breast Cancer Resistance Protein (BCRP) while M4 is a substrate of P-gp but not BCRP. Alectinib associated material 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 hours post-dose (see DETAILED PHARMACOLOGY). CNS penetration of M4 metabolite has not been investigated. In preclinical mouse xenograft models,alectinib induced tumour regression of ALK-driven cell lines and prolonged survival, including in mouse models of intracranially implanted ALK-driven tumors.

Pharmacodynamics

ECG

ECG evaluations were performed in 137 patients receiving ALECENSARO 600 mg BID in Study NP28673. The following findings were reported.

ALECENSARO 600 mg BID was associated with statistically significant ($p<0.05$) mean decreases from baseline in heart rate at ECG assessments from week 2 to week 16, inclusive, with the magnitude of the mean heart rate reduction ranging from -10.4 to -13.7 bpm.

Statistically significant ($p<0.05$) mean increases from baseline in the QTcF interval were observed during treatment with ALECENSARO 600 mg BID at the pre-dose assessments on weeks 2 and 3, but not at later time points: 5.0 msec (90% CI: 3.0, 7.1) at week 2 and 2.7 msec (90% CI: 0.8, 4.7) at week 3. Statistically significant increases from baseline in the QTcF interval were not observed at the post-dose assessments on week 2 or 3. One patient in this trial had a maximum post-baseline QTcF value of greater than 500 msec and one patient had a maximum QTcF change from baseline of greater than 60 msec.

ALECENSARO 600 mg BID was associated with statistically significant ($p<0.05$) mean increases from baseline in the PR interval at ECG assessments from week 2 to week 16, inclusive, with the magnitude of the mean PR prolongation ranging from 2.7 to 8.5 msec.

Pharmacokinetics

The pharmacokinetic parameters for alectinib and its major active metabolite (M4), have been characterized in ALK-positive NSCLC patients and healthy subjects.

Absorption: Following oral administration of 600 mg twice daily under fed conditions in ALK-positive NSCLC patients, alectinib was rapidly absorbed reaching a median T_{max} after approximately 4 to 6 hours (range of approximately 0 to 10 hours).

Based on population PK analysis of 138 ALK-positive NSCLC patients enrolled in Study NP28673, the geometric mean (coefficient of variation %) steady-state C_{max}, and $AUC_{0\text{-}12hr}$ for alectinib were approximately 665 ng/mL (44.3%), and 7430 ng*h/mL (45.7 %), respectively. The geometric mean steady-state C_{max}, and $AUC_{0\text{-}12hr}$ for M4 were approximately 246 ng/mL (45.4 %), and 2810 ng*h/mL (45.9 %), respectively.

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.

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 approximately 3-fold relative to fasted conditions (geometric mean ratio [90% CI] of alectinib C_{max}: 2.70 [2.28, 3.20], AUC_{inf}: 2.92 [2.58, 3.29].

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.

Based on a population PK analysis, the apparent volume of distribution was 4,016 L for alectinib and 10,093 L for M4, indicating extensive distribution into tissues.

Alectinib concentrations in the cerebrospinal fluid in patients with ALK-positive NSCLC approximate estimated alectinib free concentrations in the plasma.

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.

Elimination: Following administration of a single dose of ^{14}C-labeled alectinib administered orally to healthy subjects 98% of the radioactivity was excreted in feces. Eighty-four percent of the dose was excreted in the feces as unchanged alectinib and 6% of the dose was excreted as M4. Excretion of the radioactivity in urine was less than 0.5% of the administered radiolabeled dose of alectinib.

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

Special Populations and Conditions

Pediatrics: No studies have been conducted to investigate the pharmacokinetics of ALECENSARO in pediatric patients.

Geriatrics: Age does not have an effect on ALECENSARO exposure.

Hepatic Insufficiency: 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: Cmax: 1.16 [0.786 – 1.72], AUCinf: 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: Cmax: 0.981 [0.517 – 1.86], AUCinf:1.76 [0.984 – 3.15]).

No dose adjustments are required for ALECENSARO 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).

Renal Insufficiency: Negligible amounts of alectinib and the major active metabolite (M4) are excreted unchanged in urine (< 0.2 % of the dose). Based on a population pharmacokinetic analysis of 104 patients with mild renal impairment (CrCl 60 to less than 90 mL/min), 21 patients with moderate renal impairment (CrCl 30 to less than 60 mL/min) and 141 patients with normal renal function (CrCl greater than or equal to 90 mL/min), alectinib and M4 exposures were similar in patients with mild and moderate renal impairment and normal renal function. No formal pharmacokinetic study has been conducted and no population PK data was collected in patients with severe renal impairment.

STORAGE AND STABILITY

Store between 15-30°C.

Store in the original package in order to protect from light and moisture.

Keep in a safe place out of the reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

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

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form / Composition
Each ALECENSARO hard capsule contains 150 mg Alectinib (equivalent to 161.3 mg alectinib hydrochloride).

Non-medicinal ingredients (alphabetical order) of capsule content include: Carboxymethylcellulose calcium, Hydroxypropylcellulose, Lactose monohydrate, Magnesium stearate, Sodium lauryl sulfate.

Non-medicinal ingredients (alphabetical order) of capsule shell include: carnauba wax, carrageenan**,** corn starch, hypromellose**,** potassium chloride, titanium dioxide, and trace of printing ink.

Packaging

ALECENSARO is supplied as hard capsules, white, with “ALE” printed in black ink on the cap and “150 mg” printed in black ink on the body. ALECENSARO is available in bottles of 240 capsules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

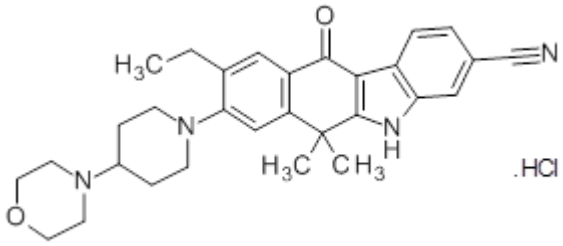
Common name: alectinib hydrochloride

Chemical name: 9-ethyl-6, 6-dimethyl-8-[4-(morpholin-4-yl)piperidin-1-yl]-11-oxo-6, 11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile hydrochloride

Molecular formula: $C_{30}H_{34}N_4O_2 \bullet HCl$.

Molecular mass: 482.62 g/mol (free base), 519.08 g/mol (hydrochloride)

Structural formula: alectinib hydrochloride



Physicochemical properties: alectinib HCl is a white to yellow or white powder with lumps with a pKa of 7.05 (base)

CLINICAL TRIALS

Crizotinib pre-treated patients

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

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 ALECENSARO orally, at the recommended dose of 600 mg twice daily.

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 ALECENSARO orally, at the recommended dose of 600 mg twice daily.

Eligibility criteria at baseline were similar for both studies and included adequate hematological, hepatic, renal and cardiac function lab parameters (see WARNINGS AND PRECAUTIONS).

In addition patients were required to have recovered from toxicities due to prior therapies (at least to Grade 2 as per NCI-CTCAE v4 for NP28673 and G1 for NP28761).

Demographic and disease characteristics for patients receiving 600 mg twice daily in phase I/II Studies are provided in Table 7.

Table 7 Demographic and Disease Characteristics of ALK-Positive Patients Treated with ALECENSARO (600 mg BID) in NP28761 and NP28673

Characteristics	NP28761 N= 87	NP28673 N=138
Sex, n (%)		
Male	39 (45)	61 (44)
Female	48 (55)	77 (56)
Age (years)		
Median (range)	54 (29-79)	52 (22-79)
Race, n (%)		
White	73 (84)	93 (67)
Asian	7 (8)	36 (26)
Other	7 (8)	9 (7)
Smoking status, n (%)		
Never smoked	54 (62)	96 (70)
Former smoker	33 (38)	39 (28)
Current smoker	0(0)	3 (2)
ECOG PS at baseline, n (%)		
0	30 (35)	44 (32)
1	48 (55)	81 (59)
2	9 (10)	13 (9)
Disease stage, n (%)		
Locally advanced	1 (1)	2 (1)
Metastatic	86 (99)	136 (99)
Histological classification, n (%)		
Adenocarcinoma	82 (94)	133 (96)
Other	5 (6)	5 (4)
Prior Chemotherapy, n (%)		
Yes	64 (74)	110 (80)
No	23 (26)	28 (20)

Characteristics	NP28761 N= 87	NP28673 N=138
Sites of Metastases, n (%)		
Lung[a]	73 (84)	119 (86)
CNS[b] (Measurable and/or Non-measurable Lesions)	52 (60)	84 (61)
CNS[c] (Measurable Lesions)	16 (18)	35 (25)
Lymph Nodes	37 (43)	53 (38)
Bone[d]	31 (36)	70 (51)
Liver	30 (34)	42 (30)
Adrenal Gland	9 (10)	11 (8)
Other	32 (37)	38 (28)

[a] Includes Pleura and Pleural Effusion; [b] Measurable and/or Non-measurable CNS lesions according to CNS RECIST assessment by IRC; [c] Measurable CNS lesions according to CNS RECIST assessment by IRC; [d] Includes Bone Marrow

Efficacy Results for NP28761

The primary endpoint was to evaluate the efficacy of ALECENSARO by Objective Response Rate (ORR) as per central Independent Review Committee (IRC) assessment using Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1. The key efficacy results are presented in Table 8.

Table 8 Summary of Efficacy from NP28761

	Alecensaro 600 mg twice daily N=87
Primary Efficacy Parameters	
ORR (IRC) in RE population Responders N (%) [95% CI] [b]	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]

CI = confidence interval; DOR = duration of response; IRC = independent review committee; NE = not estimable; ORR = Objective Response Rate; RE = response evaluable

The median duration of follow-up was 93.0 weeks (range: 0.4 to 244.1)

[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] Null hypothesis: ORR was equal to 35% versus the alternative hypothesis that the ORR was not equal to 35% (lower boundary of CI > 35%), at a two-sided alpha level of 5%

Efficacy Results for NP28673

The primary endpoint was to evaluate the efficacy of ALECENSARO 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. The key efficacy results are presented in Table 9.

Table 9 Summary of Efficacy from NP28673

	Alecensaro 600 mg twice daily N=138
Primary Efficacy Parameters	
ORR (IRC) in RE population Responders N (%) [95% CI][b]	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]

CI = confidence interval; DOR = duration of response; IRC = independent review committee; ORR = Objective Response Rate; RE = response evaluable

The median duration of follow-up was 105.50 weeks (range: 2.4 to 213.1)

[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] Null hypothesis: ORR was equal to 35% versus the alternative hypothesis that the ORR was not equal to 35% (lower boundary of CI > 35%), at a two-sided alpha level of 5%

Pooled CNS Efficacy Results for Studies NP28673 and NP28761

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.

Of these 50 patients, 34 (68%) received prior brain radiotherapy (25 more than 6 months before starting ALECENSARO, 8 between 4 weeks and 6 months of starting ALECENSARO, and 1 within 4 weeks of starting ALECENSARO).

Patients with CNS metastases or leptomeningeal disease at baseline could be enrolled in the study if any prior CNS treatment (radiotherapy and corticosteroid use) had been discontinued at

least 2 weeks before start of ALECENSARO, and any clinical symptoms of CNS disease had been stable for at least 2 weeks before start of ALECENSARO.

Table 10 Summary of the Pooled Analysis for CNS Endpoints from NP28761 and NP28673

CNS Parameters (NP28761 and NP28673)	**Alecensaro 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 DOR (IRC)	
Number of patients with events (%)	18 (56.3%)
Median (months)	11.1
[95% CI]	[7.6%; NE]

CI = confidence interval; DOR = duration of Response; IRC = independent review committee; NE= not estimable; ORR = objective response rate
The median duration of follow-up was 14 months

In 136 patients included in the phase I/II NP28761 and NP28673 studies, with measurable and/or non-measurable CNS lesions at baseline, the CNS complete response rate was 29%. A CNS partial response cannot be established in non-measurable CNS lesions per RECIST.

Treatment-naïve patients

The safety and efficacy of ALECENSARO were studied in a global randomized Phase III open label clinical trial (BO28984) in ALK-positive NSCLC patients who were treatment-naïve. 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, at the recommended dose of 250 mg orally twice daily and 152 patients randomized to the ALECENSARO arm receiving ALECENSARO 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 ALECENSARO versus crizotinib based on Progression Free survival (PFS) as per investigator assessment using RECIST 1.1. The secondary endpoints supporting the efficacy of ALECENSARO were PFS as

per central Independent Review Committee (IRC) assessment, time to CNS progression as per IRC assessment, duration of response, objective response rate (ORR), CNS-ORR as per IRC assessment, and CNS-DOR as per IRC assessment. At the data cut-off point, the overall survival (OS) secondary endpoint data was not mature.

Demographic and disease characteristics for patients receiving ALECENSARO 600 mg twice daily and crizotinib 250 mg twice daily in the pivotal phase III study are provided in Table 11.

Table 11 Demographic and Disease Characteristics of ALK-Positive Patients Treated with ALECENSARO (600 mg BID) and crizotinib (250 mg BID) in BO28984

Characteristics	ALECENSARO N=152	crizotinib N=151
Sex, n (%)		
Male	68 (45)	64 (42)
Female	84 (55)	87 (58)
Age (years)		
Median (range)	58 (25-88)	54 (18-91)
Race, n (%)		
White	76 (50)	75 (50)
Asian	69 (45)	69 (46)
Other	7 (5)	7 (5)
Smoking status, n (%)		
Active smoker	12 (8)	5 (3)
Non-smoker	92 (61)	98 (65)
Past smoker	48 (32)	48 (32)
ECOG PS at baseline, n (%)		
0 or 1	142 (93)	141 (93)
2	10 (7)	10 (7)
Disease stage, n (%)		
Locally advanced (IIIB)	4 (3)	6 (4)
Metastatic (IV)	148 (97)	145 (96)
Histological classification, n (%)		
Adenocarcinoma	136 (90)	142 (94)
Other	16 (11)	9 (6)
Prior Brain Radiation, n (%)		
Yes	26 (17)	21 (14)
No	126 (83)	130 (86)
CNS Metastases at Baseline, n (%)		
Yes	60 (40)	57 (38)
No	92 (61)	94 (62)

The trial met its primary endpoint at the primary analysis. Efficacy data are summarized in Table 12 and the Kaplan-Meier curves for investigator and IRC-assessed PFS are shown in Figures 1 and 2. The median duration of follow-up was 18.6 months (range 0.5 – 29.0) for ALECENSARO and 17.6 months (range 0.3-27.0) for crizotinib.

Table 12 Summary of Efficacy Results from Phase III study BO28984

Parameters	**Crizotinib N=151**	**Alecensaro N=152**
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	
ORR (INV)**, *** Responders n (%) [95% CI]	 114 (75.5%) [67.8; 82.1]	 126 (82.9%) [76.0; 88.5]
Duration of response (INV) Median (months) [95 % CI]	 11.1 [7.9; 13.0]	 NE [NE; NE]
CNS-ORR in patients with measurable CNS metastases at baseline (IRC) CNS responders n (%) [95% CI] CNS-CR n (%) CNS-DOR , median (months) [95% CI]	N=22 11 (50.0%) [28.2; 71.8] 1 (5%) 5.5 [2.1, 17.3]	N=21 17 (81.0%) [58.1; 94.6] 8 (38%) 17.3 [14.8, NE]
CNS-ORR in patients with measurable and non-measurable CNS metastases at baseline (IRC) CNS responders n (%) [95% CI] CNS-CR n (%) CNS-DOR , median (months) [95% CI]	N=58 15 (25.9%) [15.3; 39.0] 5 (9%) 3.7 [3.2, 6.8]	N=64 38 (59.4%) [46.4; 71.5] 29 (45%) NE [17.3, NE]

* Competing risk analysis of CNS progression, systemic progression and death as competing events
** The difference in ORR between the arms was not statistically significant (p < 0.0936)
*** 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 assessment; INV = investigator assessment; NE = not estimable; ORR = objective response rate; PFS = progression-free survival

The magnitude of PFS benefit for patients with CNS metastases at baseline (HR=0.40, 95%CI: 0.25-0.64) or without CNS metastases at baseline (HR = 0.51, 95%CI: 0.33-0.80), as determined in a subgroup analysis, suggest benefit of ALECENSARO over crizotinib in both subgroups.

Figure 1 Kaplan Meier Plot of PFS as per investigator assessment from BO28984

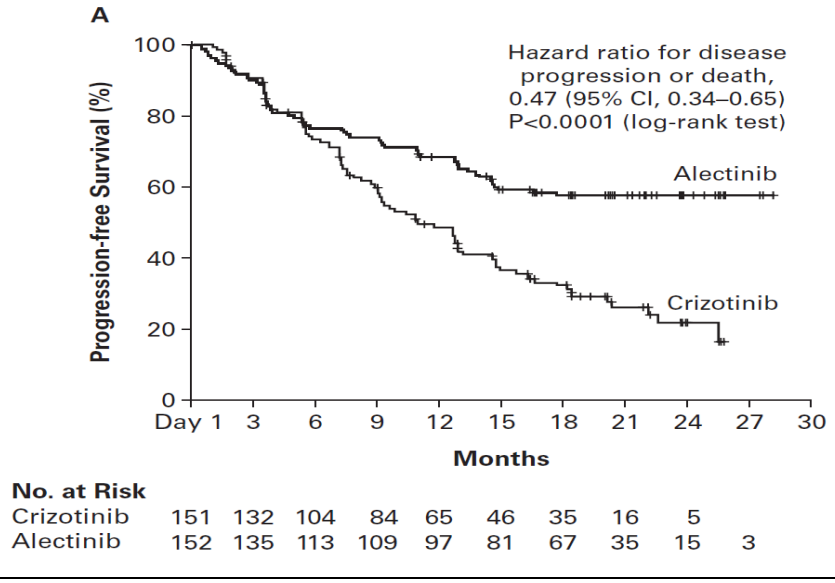
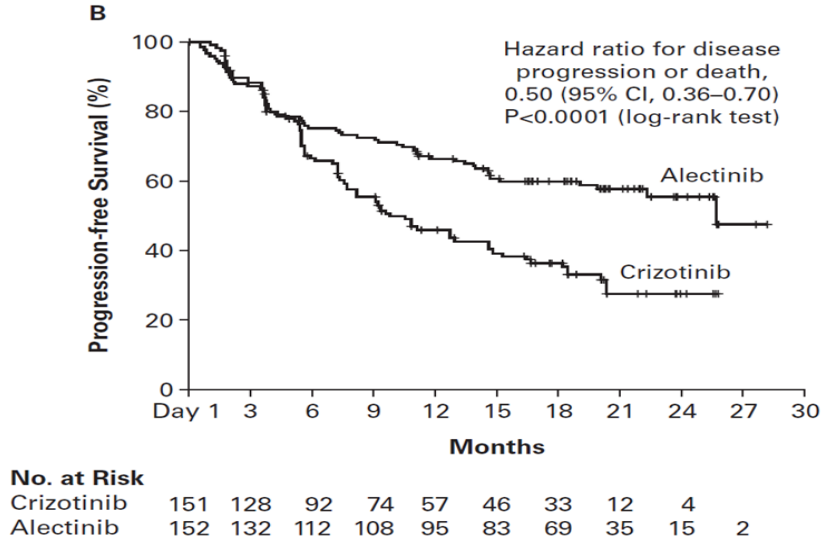


Figure 2 Kaplan Meier Plot of PFS as per central Independent Review Committee assessment from BO28984



DETAILED PHARMACOLOGY

Pharmacokinetics

Distribution

Alectinib demonstrated good penetration into various tissues in quantitative whole body autoradiography studies in rats. Organs with highest distribution were Harderian glands, adrenal glands, lungs, brown adipose tissue and liver, with tissue-to-plasma concentration (T/P) ratios at t_{max} being 345, 179, 62.1, 51.8 and 42.0, respectively. The average T/P ratios in CNS tissues (cerebrum, cerebellum and spinal cord) were 0.77 (range, 0.59-0.94) and 1.38 (range, 1.06–1.54) at 8 and 24 hours post-dose, respectively, indicating alectinib penetrating into the CNS. Tissue radioactivity disappeared over time, following a course generally comparable to that of plasma radioactivity.

Pharmacodynamics

Secondary Pharmacology

Alectinib inhibited human ether-a-go-go related gene (hERG) potassium currents with an IC_{50} of 0.45 μM (217 ng/mL). Alectinib also blocked the L-type Ca^{2+} channel current (IC_{50}: 222 ng/mL), indicating that alectinib is a calcium channel antagonist.

TOXICOLOGY

Repeated-dose Toxicity

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 human 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 was observed in monkeys at around clinically relevant exposures.

Carcinogenicity

No carcinogenicity studies have been conducted with ALECENSARO.

Mutagenicity

Alectinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay but induced a slight increase in numerical aberrations (polyploidy) in the *in vitro* cytogenetic assay using Chinese Hamster Lung (CHL) cells with metabolic activation, and micronuclei in vitro human lymphoblastoid TK6 cell and rat bone marrow micronucleus test. The mechanism of

micronucleus induction was abnormal chromosome segregation (aneugenicity), and not a clastogenicity.

Impairment of Fertility
No fertility studies in animals have been performed to evaluate the effect of ALECENSARO. No adverse effects on male and female reproductive organs were observed in general toxicology studies conducted in rats and monkeys at systemic exposures to alectinib 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.

Embryo-fetal Development
Embryo-fetal development studies have been performed in pregnant rabbits and rats. In rabbits, a maternal dose of alectinib equivalent to 2.9-times the recommended human dose of 600 mg twice-daily (based on AUC systemic exposure), caused maternal toxicity, abortion, fetal death, lower fetal body weights, and fetal rib variations. In rats, a maternal dose of alectinib equivalent to 2.7-times the recommended human dose resulted in maternal toxicity, small fetuses, retarded fetal ossification and fetal abnormalities. Total litter loss occurred in rats at a dose equivalent to 4.5 times the recommended human dose.

Phototoxicity
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.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

ALECENSARO®
Alectinib (as alectinib hydrochloride) capsules

Read this carefully before you start taking ALECENSARO and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional (doctor, pharmacist or nurse) about your medical condition and treatment and ask if there is any new information about ALECENSARO.

Serious Warnings and Precautions

ALECENSARO should only be prescribed and used under the supervision of a healthcare professional experienced with drugs used to treat cancer.

Serious side effects with ALECENSARO include:
- Life-threatening tear in the stomach or intestine (gastrointestinal perforation)
- Liver problems
- Lung problems
- Slow heart beat

ALECENSARO has not been studied in patients with severe kidney problems.

What is ALECENSARO used for?

ALECENSARO is used to treat adult patients with anaplastic lymphoma kinase (ALK)-positive, **locally advanced** (a cancer that cannot be surgically removed or treated with chemotherapy or radiation for cure) or **metastatic** (a cancer that has spread to other parts of the body) non-small cell lung cancer (NSCLC) who have gotten worse on or are unable to take crizotinib.

ALECENSARO is also used as the first treatment option for your **locally advanced** or **metastatic** ALK positive non-small cell lung cancer.

How does ALECENSARO work?
ALECENSARO belongs to a group of anti-tumor medicines which stop cancer from making new cells if the cancer is caused by a defect in a gene called anaplastic lymphoma kinase (ALK). By doing so, ALECENSARO may slow down the growth and spread of non-small cell lung cancer (NSCLC).

What are the ingredients in ALECENSARO?
Medicinal ingredients: alectinib (as alectinib hydrochloride)

Non-medicinal ingredients (in alphabetical order): carboxymethylcellulose calcium, carnauba wax, carrageenan, corn starch, hydroxypropylcellulose, hypromellose, lactose monohydrate,

magnesium stearate, potassium chloride, sodium lauryl sulfate, titanium dioxide and traces of printing ink.

ALECENSARO comes in the following dosage form and appearance:
Capsules: 150 mg (white, with "ALE" printed in black ink on the cap and "150 mg" printed in black ink on the body).

Do not use ALECENSARO if you:
- are allergic to alectinib or any of the other ingredients in ALECENSARO

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ALECENSARO. Talk about any health conditions or problems you may have, including if you:
- are intolerant to lactose, as ALECENSARO contains lactose.
- are younger than 18 years of age. The effects of ALECENSARO in people younger than 18 years old are not known.
- are taking medicine to lower your blood pressure or control your heart rate.
- have a history of slow heart rate or fainting.
- have a history of heart problems including irregular heartbeat, heart disease and heart failure.
- have a history of problems with your gut, such as inflammation in the intestines (diverticulitis), a previous tear in your stomach or intestines or cancer that has spread to your gut.
- are pregnant or plan on becoming pregnant. Do not become pregnant while taking ALECENSARO, as it can harm your unborn baby.
    - Female patients who take ALECENSARO must use effective birth control during treatment and for at least 3 months after stopping ALECENSARO.
    - Talk to your healthcare professional about birth control methods that may be right for you.
    - Tell your healthcare professional right away if you become pregnant during treatment with ALECENSARO.
- are a male patient with a female partner who is able to become pregnant.
    - Male patients should use effective birth control during treatment and for at least 3 months after stopping ALECENSARO.
    - Tell your healthcare professional right away if your partner becomes pregnant while you are receiving treatment with ALECENSARO
- are breast-feeding or planning to bread-feed. Do not breast-feed while taking ALECENSARO.

Other warnings you should know about during treatment:

Life-threatening Tear in the Stomach or Intestines
ALECENSARO may cause a tear (perforation) in the stomach or intestine. Seek immediate medical help if you experience severe stomach or abdominal pain, fever, chills, or changes in bowel habits.

Serious Liver Problems
ALECENSARO may cause liver injury. Your healthcare professional will take blood tests before you start treatment, then every 2 weeks for the first 3 months of your treatment and then less often. Tell your healthcare professional right away if you start to notice yellowing of your skin or the whites of your eyes, pain on the right side of your stomach area, dark urine, itchy skin, feeling tired, feeling less hungry than usual, nausea or vomiting or if you are bleeding or bruising more easily.

Serious Lung Problems
ALECENSARO may cause severe or life-threatening swelling of the lungs during treatment. The signs may be similar to those from your lung cancer. Seek immediate medical help if you have any new or worsening lung problems including difficulty in breathing, shortness of breath, or cough with or without mucous, or fever.

Slow Heart Beat
ALECENSARO may cause very slow heartbeats. Your healthcare professional will check your heart rate and blood pressure during treatment with ALECENSARO. Tell your healthcare professional right away if you feel dizzy or faint or have abnormal heartbeats.

Serious Muscle Problems
Muscle problems are common with ALECENSARO and can be severe. Your healthcare professional will do blood tests at least every 2 weeks for the first month and as needed during treatment with ALECENSARO. Tell your healthcare professional right away if you get new or worsening signs and symptoms of muscle problems, including unexplained muscle pain or muscle pain that does not go away, tenderness, or weakness.

Serious Kidney Problems
ALECENSARO may cause severe or life-threatening kidney problems. Tell your healthcare professional right away if you have a change in the amount or colour of your urine, or if you get new or worsening swelling in your legs or feet.

Sensitivity to Sunlight
ALECENSARO can cause your skin to become very sensitive to sunlight. You should limit your exposure to the sun and tanning beds while you are taking ALECENSARO and for 7 days after stopping. If sun exposure is unavoidable a broad specturm UVA/UVB suncreen and lipbalm must be used to protect against sunburn.

Driving or using machines
ALECENSARO may influence your ability to drive and use machines. If you feel dizzy, weak, or tired, or have problems with your eyes while taking ALECENSARO, do no drive or use tools or machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ALECENSARO:

- Digoxin, used for heart problems
- Dabigatran, used to thin the blood to prevent blood clots
- Methotrexate, used to treat cancer and immune system disorders
- Drugs used to lower heart rate
- St. John's wort, a herbal medicine used to treat depression
- Grapefruit, grapefruit juice, products containing grapefruit extract, star fruit, pomegranate, Seville oranges or other similar fruit

How to take ALECENSARO:
- Always take ALECENSARO exactly as your doctor or pharmacist has told you. Check with your healthcare professional if you are not sure.
- ALECENSARO is taken by mouth. Swallow each capsule whole. Do not open or dissolve the capsules.
- You should take ALECENSARO with food.

Usual dose:

The recommended dose of ALECENSARO is 600 mg (4 capsules) taken twice daily (total of 8 capsules, 1200 mg per day).

Sometimes your doctor may lower your dose, stop your treatment for a short time or stop your treatment completely if you feel unwell.

Overdose:

If you think you have taken too much ALECENSARO, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take ALECENSARO:
- Take your next dose at your regular time.
- Do not take a double dose to make up for a missed dose.

Vomiting:
If you vomit (throw up) after taking ALECENSARO, do not take an extra dose of ALECENSARO, just take your next dose at the usual time.

What are possible side effects from using ALECENSARO?

These are not all the possible side effects you may experience when taking ALECENSARO. If you experience any side effects not listed here, contact your healthcare professional. Please also see the warnings above.

Side effects of ALECENSARO may include:

- constipation
- diarrhea
- nausea
- vomiting
- abnormal or metallic taste in the mouth
- inflammation of the mucous membrane of the mouth
- weight gain
- headache
- dizziness
- sensitivity to sunlight
- problems with your eyes such as blurred vision, loss of sight, black dots or white spots in your vision, and seeing double.
- dry skin
- rash
- hair loss
- itching
- numbness and tingling in the hands and feet
- muscle ache and pain, joint pain
- fatigue
- swelling caused by fluid build-up in the body (edema)

ALECENSARO can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON **Serious Muscle Problems:** unexplained muscle pain or muscle pain that does not go away, tenderness, or weakness		✓	
Serious Anemia: fatigue, dizziness, fast heart rate, shortness of breath		✓	
Slow Heart Beat: dizziness, lightheadedness, slow heart beat, fainting		✓	
UNCOMMON **Life-threatening Tear in the Stomach or Intestines:** severe stomach or abdominal pain, fever, chills, or changes in bowel habits, death.			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Serious Lung Problems: new or worsening difficulty breathing, shortness of breath, cough with or without mucous, or fever.			✓
Serious Liver Problems: yellowing of your skin or the whites of your eyes, pain on the right side of your stomach area, dark urine, itchy skin, feeling tired, feeling less hungry than usual, nausea or vomiting, bleeding or bruising more easily than normal.		✓	
Serious Kidney Problems: change in the amount or colour of your urine, new or worsening swelling in your legs or feet.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store ALECENSARO between 15-30°C.
- Store in the original package in order to protect from light and moisture.
- Keep out of reach and sight of children.
- Do not take this medicine after the expiry date which is stated on the bottle after "EXP". The expiry date refers to the last day of that month.
- Do not throw away any unused medicine in the garbage or down the drain or toilet. Therefore, ask your pharmacist how to best dispose of medicines that you no longer require. These measures will help to protect the environment.

If you want more information about ALECENSARO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); the manufacturer's website (www.rochecanada.com), or by calling 1-888-762-4388.

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