Five patients (0.9%) in the pooled safety population discontinued ALECENSA due to ILD/pneumonitis. The median time-to-onset of Grade 3 or higher ILD/pneumonitis was 2.1 months (range: 0.6 months to 3.6 months).

Promptly investigate for ILD/pneumonitis in any patient who presents with worsening of respiratory symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, and fever). Immediately withhold ALECENSA treatment in patients diagnosed with ILD/pneumonitis and permanently discontinue ALECENSA if no other potential causes of ILD/pneumonitis have been identified *[see Dosage and Administration (2.4) and Adverse Reactions (6)]*.

5.3 Renal Impairment

Renal impairment, including fatal cases, occurred in patients treated with ALECENSA.

In the pooled safety population *[see Adverse Reactions (6.1)]*, renal impairment occurred in 12% of patients treated with ALECENSA, including Grade ≥ 3 in 1.7% of patients, of which 0.4% were fatal events. The median time to Grade ≥ 3 renal impairment was 3.7 months (range 0.5 to 31.8 months). Dosage modifications for renal impairment were required in 2.4% of patients.

Permanently discontinue ALECENSA for Grade 4 renal toxicity. Withhold ALECENSA for Grade 3 renal toxicity until recovery to less than or equal to 1.5 times ULN, then resume at reduced dose *[see Dosage and Administration (2.4)]*.

5.4 Bradycardia

Symptomatic bradycardia occurred in patients treated with ALECENSA.

In the pooled safety population *[see Adverse Reactions (6.1)]*, bradycardia occurred in 11% of patients treated with ALECENSA. Twenty percent of 521 patients treated with ALECENSA, for whom serial electrocardiograms (ECGs) were available, had post-dose heart rates of less than 50 beats per minute (bpm).

Monitor heart rate and blood pressure regularly. For asymptomatic bradycardia dose modification is not required. For symptomatic bradycardia that is not life-threatening, withhold ALECENSA until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm and evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If bradycardia is attributable to a concomitant medication, resume ALECENSA at a reduced dose (see Table 2) upon recovery to asymptomatic bradycardia or to a heart rate of ≥ 60 bpm, with frequent monitoring as clinically indicated.

Permanently discontinue ALECENSA in cases of life-threatening bradycardia if no contributing concomitant medication is identified *[see Dosage and Administration (2.4)]*. Permanently discontinue ALECENSA for recurrence of life-threatening bradycardia.

5.5 Severe Myalgia and Creatine Phosphokinase (CPK) Elevation

Severe myalgia and creatine phosphokinase (CPK) elevation occurred in patients treated with ALECENSA.

In the pooled safety population *[see Adverse Reactions (6.1)]*, myalgia (including muscle- and musculoskeletal-related reactions) occurred in 31% of patients treated with ALECENSA, including Grade ≥ 3 in 0.8% of patients. Dosage modifications for myalgia events were required in 2.1% of patients.

In the pooled safety population, of the 491 patients with CPK laboratory data available, elevated CPK occurred in 56% of patients treated with ALECENSA, including 6% Grade ≥ 3. The median time to Grade ≥ 3 CPK elevation was 15 days (interquartile range - 15 –337 days). Dosage modifications for elevation of CPK occurred in 5% of patients.

In the ALINA study, elevated CPK occurred in 77% of 128 patients with CPK laboratory data, including 6% Grade ≥ 3 elevations.

Advise patients to report any unexplained muscle pain, tenderness, or weakness. Assess CPK levels every 2 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 Dosage and Administration (2.4)]*.

5.6 Hemolytic Anemia

Hemolytic anemia occurred in patients treated with ALECENSA.

Hemolytic anemia was initially reported with ALECENSA in the postmarketing setting, including cases associated with a negative direct antiglobulin test (DAT) result. Assessments for the determination of hemolytic anemia were subsequently collected in the ALINA study, where hemolytic anemia was observed in 3.1% of patients treated with ALECENSA. If hemolytic anemia is suspected, withhold ALECENSA and initiate appropriate laboratory testing. If hemolytic anemia is confirmed, consider resuming at a reduced dose upon resolution or permanently discontinue ALECENSA *[see Dosage and Administration (2.4)]*.

5.7 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, ALECENSA can cause fetal harm when administered to pregnant women. Oral administration of alectinib to pregnant rats and rabbits during the period of organogenesis resulted in embryo-fetal toxicity and abortion at maternally toxic doses with exposures approximately 2.7-fold those observed in humans with alectinib 600 mg twice daily. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with ALECENSA and for 5 weeks following the last dose *[see Use in Specific Populations (8.1 and 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Interstitial Lung Disease (ILD)/Pneumonitis *[see Warnings and Precautions (5.2)]*
- Renal Impairment *[see Warnings and Precautions (5.3)]*
- Bradycardia *[see Warnings and Precautions (5.4)]*
- Severe Myalgia and Creatine Phosphokinase (CPK) Elevation *[see Warnings and Precautions (5.5)]*
- Hemolytic Anemia *[see Warnings and Precautions (5.6)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to ALECENSA as a single agent at 600 mg orally twice daily in 533 patients in Studies NP28761, NP28673, ALEX and ALINA *[see Clinical Studies (14)]*. Among 533 patients who received ALECENSA, 75% were exposed for 6 months or longer and 64% were exposed for greater than one year. In this pooled safety population, the most common (≥ 20%) adverse reactions were hepatotoxicity (41%), constipation (39%), fatigue (36%), myalgia (31%), edema (29%), rash (23%) and cough (21%). The most common (≥ 2%) Grade 3 or 4 laboratory abnormalities were increased CPK (6%), decreased hemoglobin (4.4%), increased ALT (4.2%), increased bilirubin (4.0%) and increased AST (3.4%).

Adjuvant Treatment of Resected ALK-Positive NSCLC

The safety of ALECENSA was evaluated in ALINA, a multi-center, open-label, randomized trial for the adjuvant treatment of patients with resected ALK-positive NSCLC [*see Clinical Studies (14.1)*]. At the time of DFS analysis, the median duration of exposure was 23.9 months for ALECENSA and 2.1 months for platinum-based chemotherapy.

Serious adverse reactions occurred in 13% of patients treated with ALECENSA; the most frequent serious adverse reactions (≥ 1%) were pneumonia (3.9%), appendicitis (3.1%), and acute myocardial infarction (1.6%). Permanent discontinuation of ALECENSA due to an adverse event occurred in 5% of patients; the most frequent adverse reactions (≥ 1%) that led to treatment discontinuation were pneumonitis and hepatotoxicity.

Dosage interruptions of ALECENSA due to an adverse reaction occurred in 27% of patients. Adverse reactions which required dosage interruption in ≥ 2% of patients included hepatotoxicity, increased blood CPK, COVID-19, myalgia, abdominal pain, and pneumonia.

Dose reductions of ALECENSA due to an adverse reaction occurred in 26% of patients. Adverse reactions which required dose reductions in ≥ 2% of patients included hepatotoxicity, increased blood CPK, rash, bradycardia and myalgia.

Table 4 and 5 summarize the common adverse reactions and laboratory abnormalities observed in ALINA.

Table 4: Adverse Reactions (≥ 10%) in Patients Treated with ALECENSA in ALINA

Adverse Reaction	ALECENSA N=128		Chemotherapy N=120	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hepatobiliary System Disorders				
Hepatotoxicity[a]	61	4.7*	13	0
Gastrointestinal Disorders				
Constipation	42	0.8*	25	0.8*
Abdominal pain[b]	13	0	10	1.7*
Diarrhea[c]	13	0.8*	9	1.7*
Musculoskeletal				
Myalgia[d]	34	0.8*	1.7	0
Infections and Infestations				
COVID-19	29	0	0.8	0
General Disorders and Administration Site Conditions				
Fatigue[e]	25	0.8*	28	4.2*
Edema[f]	16	0	1.7	0
Skin and Subcutaneous Tissue Disorders				
Rash[g]	23	1.6*	10	0
Respiratory System Disorders				
Cough[h]	20	0.8*	3.3	0
Dyspnea[i]	13	0.8*	2.5	0
Renal				
Renal Impairment[j]	16	0.8*	9	0

Nervous System Disorders				
Dysgeusia[k]	13	0	3.3	0
Headache	11	0	7	0
Investigations				
Increased weight	13	0.8*	0.8	0
Cardiac Disorders				
Bradycardia[l]	12	0	0	0

Based on NCI CTCAE v5.0

* All events are Grade 3.

[a] Includes increased alanine aminotransferase, increased aspartate aminotransferase, increased bile acids, increased conjugated bilirubin, increased blood bilirubin, increased unconjugated blood bilirubin, increased gamma-glutamyltransferase, hepatotoxicity, hyperbilirubinemia, increased liver function test, ocular icterus and increased transaminases.

[b] Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort and gastrointestinal pain.

[c] Includes colitis and diarrhea.

[d] Includes muscle fatigue, muscular weakness, musculoskeletal chest pain, musculoskeletal stiffness and myalgia.

[e] Includes asthenia and fatigue.

[f] Includes edema, face edema, localized edema, peripheral edema, face swelling and peripheral swelling.

[g] Includes acneiform dermatitis, bullous dermatitis, drug eruption, eczema, rash, erythematous rash, maculo-papular rash, papular rash, seborrheic dermatitis, urticaria and xeroderma.

[h] Includes cough and productive cough.

[i] Includes dyspnea and exertional dyspnea.

[j] Includes azotemia, increased blood creatinine, decreased renal creatinine clearance, decreased glomerular filtration rate, hypercreatininemia, renal impairment and renal failure.

[k] Includes dysgeusia and taste disorder.

[l] Includes bradycardia and sinus bradycardia.

Clinically significant adverse reactions in < 10% of patients who received ALECENSA in ALINA: nausea (8%), vomiting (7%), vision disorders (4.7%; includes blurred vision, visual acuity reduced and photopsia), stomatitis (4.7%; includes stomatitis and mouth ulceration), photosensitivity reaction (3.9%) and pneumonitis (2.3%).

Table 5: Worsening in Laboratory Values from Baseline Occurring in ≥ 20% of Patients in Treated with ALECENSA in ALINA

Parameter	ALECENSA N=128		Chemotherapy N=120	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Chemistry				
Increased CPK	77	8	8	1.7*
Increased AST	75	0.8*	25	0
Increased bilirubin	68	2.3*	4.2	0
Increased alkaline phosphatase	64	0	14	0
Increased ALT	57	2.3*	28	0
Increased creatinine	41	0	23	0
Increased uric acid	30	0	19	0
Hematology				
Decreased hemoglobin	69	0	67	0.8*

Based on NCI CTCAE v5.0
*All events were Grade 3

Previously Untreated Metastatic ALK-Positive NSCLC

The safety of ALECENSA was evaluated in 152 patients with ALK-positive NSCLC in the ALEX study. The median duration of exposure to ALECENSA was 17.9 months. Patient characteristics of the ALEX study population (n=303) were: median age 56 years, age less than 65 (77%), female (56%), Caucasian (50%), Asian (46%), adenocarcinoma histology (92%), never smoker (63%), and ECOG PS 0 or 1 (93%).

Serious adverse reactions occurred in 28% of patients treated with ALECENSA; serious adverse reactions reported in 2% or more of patients treated with ALECENSA were pneumonia (4.6%), and renal impairment (3.9%). Grade ≥ 3 adverse events were reported for 41% of patients in the ALECENSA arm. Fatal adverse reactions occurred in 3.3% of patients treated with ALECENSA; these were renal impairment (2 patients), sudden death, cardiac arrest, and pneumonia (1 patient each). Permanent discontinuation of ALECENSA for adverse reactions occurred in 11% of patients. Adverse drug reactions that led to discontinuation of ALECENSA in 1% or more of patients were renal impairment (2.0%), hyperbilirubinemia (1.3%), increased ALT (1.3%), and increased AST (1.3%). Dosage interruptions of ALECENSA due to an adverse reaction occurred in 20% of patients. Adverse reactions which required dosage interruption in > 2% of patients included increased ALT, pneumonia. Dose reductions of ALECENSA due to an adverse reaction occurred in 17% of patients. Adverse reactions which required dose reductions in > 2% of patients included hyperbilirubinemia, increased AST and increased ALT.

Tables 6 and 7 summarize the common adverse reactions and laboratory abnormalities observed in ALEX.

Table 6: Adverse Drug Reactions (>10% for all NCI CTCAE Grades or ≥2% for Grades 3-4) in Patients Treated with ALECENSA in ALEX

Adverse Reaction	ALECENSA N=152		Crizotinib N=151	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Constipation	34	0	33	0
Nausea	14	0.7	48	3.3
Diarrhea	12	0	45	2.0
General				
Fatigue[a]	26	1.3	23	0.7
Edema[b]	22	0.7	34	0.7
Musculoskeletal				
Myalgia[c]	23	0	4.0	0
Skin				
Rash[d]	15	0.7	13	0
Cardiac				
Bradycardia[e]	11	0	15	0
Renal				
Renal impairment[f]	12	3.9*	0	0

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; SOC = System Organ Class.

[a] Includes fatigue and asthenia.

[b] Includes peripheral edema, edema, eyelid edema, localized edema, and face edema.

[c] Includes myalgia and musculoskeletal pain.

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

[e] Includes reported cases of bradycardia and sinus bradycardia but is not based on serial ECG assessment.

[f] Includes increased blood creatinine, creatinine renal clearance decreased, glomerular filtration rate decreased, and acute kidney injury.

* Includes two Grade 5 events.

The following additional clinically significant adverse drug reactions were observed in patients treated with ALECENSA: weight gain (9.9%), vomiting (7%), photosensitivity reaction (5.3%), vision disorders (4.6%; includes blurred vision, visual impairment, vitreous floaters reduced visual acuity and diplopia), stomatitis (3.3%), dysgeusia (3.3%; includes hypogeusia), interstitial lung disease (1.3%), and drug-induced liver injury (1.3%).

Table 7: Worsening in Laboratory Values Occurring in > 10% of Patients in ALEX

Parameter	ALECENSA N= 152		Crizotinib N=151	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Chemistry				
Hyperbilirubinemia[a]	54	5	4.7	0
Increased AST[b]	50	6	56	11
Increased alkaline phosphatase[c]	50	0	44	0
Increased ALT[c]	40	6	62	16
Increased creatinine[c,d]	38	4.1	23	0.7
Increased CPK[e]	37	2.8	52	1.4
Hypocalcemia[a]	29	0	61	1.4
Hyperglycemia[f]	22	2.2	19	2.3
Hyponatremia[g]	18	6	20	4.1
Hypokalemia[c]	17	2	12	0.7
Hypoalbuminemia[h]	14	0	57	3.4
Hyperkalemia[c]	12	1.4	16	1.4
Hypophosphatemia[i]	9	1.4	25	2.7
Increased gamma glutamyl transferase[j]	7	0.7	39	4.1
Hematology				
Anemia[c]	62	7	36	0.7
Lymphopenia[a]	14	1.4	34	4.1
Neutropenia[c]	14	0	36	7

Note: Based on National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.
Excludes patients with no post-baseline lab assessments.
[a] n=147 for alectinib (with baseline values missing for 1 of these patients), n=148 for crizotinib.
[b] n=147 for alectinib (with baseline values missing for 2 of these patients), n=148 for crizotinib.
[c] n=147 for alectinib, n=148 for crizotinib.
[d] Only patients with creatinine increases based on ULN definition.
[e] n=143 for alectinib (with baseline values missing for 14 of these patients), n=143 for crizotinib (with baseline values missing for 13 of these patients).
[f] n=134 for alectinib (with baseline values missing for 18 of these patients), n=131 for crizotinib (with baseline values missing for 8 of these patients).
[g] n=147 for alectinib, n=148 for crizotinib (with baseline values missing for 1 of these patients).
[h] n=146 for alectinib (with baseline values missing for 1 of these patients), n=148 for crizotinib (with baseline values missing for 1 of these patients).
[i] n=145 for alectinib (with baseline values missing for 2 of these patients), n=148 for crizotinib (with baseline values missing for 4 of these patients).
[j] n=143 for alectinib (with baseline values missing for 4 of these patients), n=148 (with baseline values missing for 5 of these patients).

Metastatic ALK-Positive NSCLC Previously Treated with Crizotinib

The safety of ALECENSA was evaluated in 253 patients with ALK-positive non-small cell lung cancer (NSCLC) treated with ALECENSA in two clinical trials, Studies NP28761 and NP28673. The median duration of exposure to ALECENSA was 9.3 months. One hundred sixty-nine patients (67%) were exposed to ALECENSA for more than 6 months, and 100 patients (40%) for more than one year. The population characteristics were: median age 53 years, age less than 65 (86%), female (55%), White (74%), Asian (18%), NSCLC adenocarcinoma histology (96%), never or former smoker (98%), ECOG Performance Status (PS) 0 or 1 (91%), and prior chemotherapy treatment (78%).

Serious adverse reactions occurred in 19% of patients; the most frequently reported serious adverse reactions were pulmonary embolism (1.2%), dyspnea (1.2%), and hyperbilirubinemia (1.2%). Fatal adverse reactions occurred in 2.8% of patients and included hemorrhage (0.8%), intestinal perforation (0.4%), dyspnea (0.4%),

pulmonary embolism (0.4%), and endocarditis (0.4%). Permanent discontinuation of ALECENSA for adverse reactions occurred in 6% of patients. The most frequent adverse reactions that led to permanent discontinuation were hyperbilirubinemia (1.6%), increased ALT levels (1.6%), and increased AST levels (1.2%). Overall, 23% of patients initiating treatment at the recommended dose required at least one dose reduction. The median time to first dose reduction was 48 days. The most frequent adverse reactions that led to dose reductions or interruptions were elevations in bilirubin (6%), CPK (4.3%), ALT (4.0%), AST (2.8%), and vomiting (2.8%).

Tables 8 and 9 summarize the common adverse reactions and laboratory abnormalities observed in Studies NP28761 and NP28673.

Table 8: Adverse Reactions in ≥ 10% (All Grades) or ≥ 2% (Grades 3–4) of Patients in Studies NP28761 and NP28673

Adverse Reactions	ALECENSA N=253	
	All Grades (%)	Grades 3–4 (%)*
Fatigue[a]	41	1.2
Constipation	34	0
Edema[b]	30	0.8
Myalgia[c]	29	1.2
Cough	19	0
Rash[d]	18	0.4
Nausea	18	0
Headache	17	0.8
Diarrhea	16	1.2
Dyspnea	16	3.6[e]
Back pain	12	0
Vomiting	12	0.4
Increased weight	11	0.4
Vision disorder[f]	10	0

* Per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
[a] Includes fatigue and asthenia.
[b] Includes peripheral edema, edema, generalized edema, eyelid edema, and periorbital edema.
[c] Includes myalgia and musculoskeletal pain.
[d] Includes rash, maculopapular rash, acneiform dermatitis, erythema, generalized rash, papular rash, pruritic rash, and macular rash.
[e] Includes one Grade 5 event.
[f] Includes blurred vision, vitreous floaters, visual impairment, reduced visual acuity, asthenopia, and diplopia.

An additional clinically significant adverse drug reaction was photosensitivity, which occurred in 9.9% of patients exposed to ALECENSA in Studies NP28761 and NP28673. Patients were advised to avoid sun exposure and to use broad-spectrum sunscreen. The incidence of Grade 2 photosensitivity was 0.4%; the remaining events were Grade 1 in severity.

Table 9: Treatment-Emergent Worsening in Laboratory Values Occurring in > 20% of Patients in Studies NP28761 and NP28673

Parameter	ALECENSA N=250	
	All Grades (%)	Grades 3–4 (%)*
Chemistry		
Increased AST	51	3.6
Increased Alkaline Phosphatase	47	1.2
Increased CPK[a]	43	4.6
Hyperbilirubinemia	39	2.4
Hyperglycemia[b]	36	2.0
Increased ALT	34	4.8
Hypocalcemia	32	0.4
Hypokalemia	29	4.0
Increased Creatinine[c]	28	0
Hypophosphatemia	21	2.8
Hyponatremia	20	2.0
Hematology		
Anemia	56	2.0
Lymphopenia[d]	22	4.6

* Per CTCAE version 4.0
[a] n=218 for CPK (with baseline values missing for 91 of these patients).
[b] n=152 for fasting blood glucose (with baseline values missing for 5 of these patients).
[c] Only patients with creatinine increases based on ULN definition.
[d] n=217 for lymphocytes (with baseline values missing for 5 of these patients).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, ALECENSA can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on ALECENSA use in pregnant women.

Administration of alectinib to pregnant rats and rabbits by oral gavage during the period of organogenesis resulted in embryo-fetal toxicity and abortion at maternally toxic doses with exposures approximately 2.7-fold those observed in humans treated with alectinib at 600 mg twice daily *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In a preliminary rabbit embryo-fetal study, administration of alectinib by oral gavage during the period of organogenesis resulted in abortion or complete embryo-fetal mortality at a maternally toxic dose of 27 mg/kg/day (approximately 2.9-fold the estimated area under the curve ($AUC_{0\text{-}24h,ss}$) in humans treated with alectinib 600 mg twice daily) in three of six pregnant rabbits. The remaining three pregnant rabbits in this group had few live fetuses, decreased fetal and placental weights, and retroesophageal subclavian artery. In a rat preliminary embryo-fetal development study, administration of alectinib during organogenesis resulted in complete litter loss in all pregnant rats at 27 mg/kg/day (approximately 4.5-fold the estimated $AUC_{0\text{-}24h,ss}$ in humans treated with alectinib 600 mg twice daily). Doses greater than or equal to 9 mg/kg/day (approximately 2.7-fold the estimated human $AUC_{0\text{-}24h,ss}$ in humans treated with alectinib 600 mg twice daily), resulted in maternal toxicity as well as developmental toxicities including decreased fetal weight, dilated ureter, thymic cord, small ventricle and thin ventricle wall, and reduced number of sacral and caudal vertebrae.

8.2 Lactation

Risk Summary

There are no data on the presence of alectinib or its metabolites in human milk, the effects of alectinib on the breastfed child, or its effects on milk production. Because of the potential for serious adverse reactions in breastfed children from alectinib, advise a lactating woman not to breastfeed during treatment with ALECENSA and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

ALECENSA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating ALECENSA *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with ALECENSA and for 5 weeks after the last dose *[see Use in Specific Populations (8.1)]*.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with ALECENSA and for 3 months following the last dose *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of ALECENSA in pediatric patients have not been established.

Animal Data

Juvenile animal studies have not been conducted using alectinib. In general toxicology studies, treatment of rats with doses of alectinib resulting in exposures greater than or equal to approximately 4.5-fold those in humans treated with alectinib at 600 mg twice daily resulted in changes in the growing teeth and bones. Findings in teeth included discoloration and changes in tooth size along with histopathological disarrangement of the

ameloblast and odontoblast layers. There were also decreases in the trabecular bone and increased osteoclast activity in the femur and sternum.

8.5 Geriatric Use

Nineteen percent of the 533 patients studied in NP28761, NP28673, ALEX and ALINA were 65 years of age and older (3.2% were 75 years of age and older). No overall differences in effectiveness were observed based on age. Exploratory analysis suggests a higher incidence of serious adverse events (38% vs 25%), more frequent adverse events leading to treatment discontinuations (18% vs 6%) and dose modifications (48% vs 35%) in patients 65 years or older as compared to those younger than 65 years.

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment. The safety of ALECENSA in patients with severe renal impairment (creatinine clearance less than 30 mL/min) or end-stage renal disease has not been studied *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

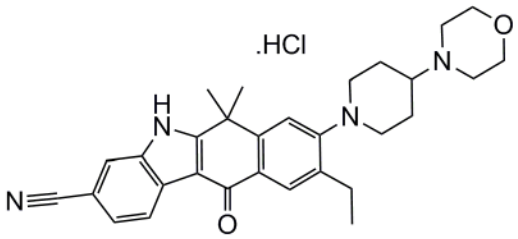
No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Increased exposure of alectinib occurred in patients with severe hepatic impairment (Child-Pugh C). The recommended dose of ALECENSA in patients with severe hepatic impairment (Child-Pugh C) is 450 mg orally twice daily *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

No experience with overdose is available. There is no specific antidote for overdose with ALECENSA. Alectinib and its major active metabolite M4 are > 99% bound to plasma proteins; therefore, hemodialysis is likely to be ineffective in the treatment of overdose.

11 DESCRIPTION

ALECENSA (alectinib) is a kinase inhibitor for oral administration. The molecular formula for alectinib is $C_{30}H_{34}N_4O_2$ • HCl. The molecular weight is 482.62 g/mol (free base form) and 519.08 g/mol (hydrochloride salt). Alectinib is described chemically as 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. The chemical structure of alectinib is shown below:



Alectinib HCl is a white to yellow white powder or powder with lumps with a pKa of 7.05 (base).

ALECENSA is supplied as hard capsules containing 150 mg of alectinib (equivalent to 161.33 mg alectinib HCl) and the following inactive ingredients: lactose monohydrate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate, and carboxymethylcellulose calcium. The capsule shell contains hypromellose, carrageenan, potassium chloride, titanium dioxide, corn starch, and carnauba wax. The printing ink contains red iron oxide (E172), yellow iron oxide (E172), FD&C Blue No. 2 aluminum lake (E132), carnauba wax, white shellac, and glyceryl monooleate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alectinib is a tyrosine kinase inhibitor that targets ALK and RET. In nonclinical studies, alectinib inhibited ALK phosphorylation and ALK-mediated activation of the downstream signaling proteins STAT3 and AKT, and decreased tumor cell viability in multiple cell lines harboring ALK fusions, amplifications, or activating mutations. The major active metabolite of alectinib, M4, showed similar in vitro potency and activity.

Alectinib and M4 demonstrated in vitro and in vivo activity against multiple mutant forms of the ALK enzyme, including some mutations identified in NSCLC tumors in patients who have progressed on crizotinib.

In mouse models implanted with tumors carrying ALK fusions, administration of alectinib resulted in antitumor activity and prolonged survival, including in mouse models implanted intracranially with ALK-driven tumor cell lines.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The ability of alectinib to prolong the QT interval was assessed in 221 patients administered ALECENSA 600 mg twice daily in clinical studies. ALECENSA did not prolong the QTc (QT corrected for heart rate) interval to any clinically relevant extent. One patient 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.

12.3 Pharmacokinetics

The pharmacokinetics of alectinib and its major active metabolite M4 have been characterized in patients with ALK-positive NSCLC and healthy subjects.

In patients with ALK-positive NSCLC, the geometric mean (coefficient of variation %) steady-state maximal concentration ($C_{max,ss}$) for alectinib was 665 ng/mL (44%) and for M4 was 246 ng/mL (45%) with peak to trough concentration ratio of 1.2. The geometric mean steady-state area under the curve from 0 to 12 hours ($AUC_{0-12h,ss}$) for alectinib was 7,430 ng*h/mL (46%) and for M4 was 2,810 ng*h/mL (46%). Alectinib exposure is dose proportional across the dose range of 460 mg to 900 mg (i.e., 0.75 to 1.5 times the approved recommended dosage) under fed conditions. Alectinib and M4 reached steady-state concentrations by day 7. The geometric mean accumulation was approximately 6-fold for both alectinib and M4.

Absorption

Alectinib reached maximal concentrations at 4 hours following administration of ALECENSA 600 mg twice daily under fed conditions in patients with ALK-positive NSCLC.

The absolute bioavailability of alectinib was 37% (90% CI: 34%, 40%) under fed conditions.

A high-fat, high-calorie meal increased the combined exposure (AUC_{0-inf}) of alectinib plus M4 by 3.1-fold (90% CI: 2.7, 3.6) following oral administration of a single 600 mg dose of ALECENSA.

Distribution

The apparent volume of distribution is 4,016 L for alectinib and 10,093 L for M4.

Alectinib and M4 are bound to human plasma proteins greater than 99%, independent of drug concentration.

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

In vitro studies suggest that alectinib is not a substrate of P-glycoprotein (P-gp), but M4 is a substrate of P-gp. Alectinib and M4 are not substrates of breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP) 1B1, or OATP1B3.

Elimination

The apparent clearance (CL/F) is 81.9 L/hour for alectinib and 217 L/hour for M4. The geometric mean elimination half-life is 33 hours for alectinib and 31 hours for M4 in patients with ALK-positive NSCLC.

Metabolism

Alectinib is metabolized by CYP3A4 to its major active metabolite M4. The geometric mean metabolite/parent exposure ratio at steady-state is 0.40. M4 is subsequently metabolized by CYP3A4. Alectinib and M4 were the main circulating moieties in plasma, constituting 76% of the total radioactivity.

Excretion

Ninety-eight percent of the radioactivity was excreted in feces following oral administration of a single radiolabeled dose of alectinib under fed conditions. 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 radioactivity in urine was less than 0.5% of administered radiolabeled dose of alectinib.

Specific Populations

Age (21 to 83 years), body weight (38 to 128 kg), mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin 1 to ≤ 1.5 × ULN and AST any value), mild to moderate renal impairment (creatinine clearance 30 to 89 mL/min), race (White, Asian, and Other), and sex had no clinically meaningful effect on the systemic exposure of alectinib and M4. The pharmacokinetics of alectinib have not been studied in patients with severe renal impairment (creatinine clearance < 30 mL/min), or end-stage renal disease.

Hepatic Impairment: Following administration of a single oral dose of 300 mg ALECENSA, the geometric mean ratio [90% confidence interval] for the combined AUC_{inf} of alectinib and M4 in subjects with moderate hepatic impairment (Child-Pugh B) was 1.36 [0.947, 1.96] and in subjects with severe hepatic impairment (Child-Pugh C) was 1.76 [0.984, 3.15] as compared to that in subjects with normal hepatic function. The combined C_{max} of alectinib and M4 was comparable among the three groups. No dose adjustment is recommended for patients with mild or moderate hepatic impairment. The recommended dose of ALECENSA in patients with severe hepatic impairment is 450 mg orally twice daily *[see Dosage and Administration (2.3) and Use in Specific Populations (8.7)]*.

Drug Interactions

Effect of Other Drugs on Alectinib

No clinically meaningful effect on the combined exposure of alectinib plus M4 was observed in clinical studies following co-administration of ALECENSA with a strong CYP3A inhibitor (posaconazole), a strong CYP3A inducer (rifampin), or an acid-reducing agent (esomeprazole).

Effect of Alectinib on Other Drugs

No clinically meaningful effect on the exposure of midazolam (sensitive CYP3A substrate) or repaglinide (sensitive CYP2C8 substrate) is expected following co-administration with ALECENSA.

In vitro studies suggest that alectinib and M4 do not inhibit CYP1A2, 2B6, 2C9, 2C19 or 2D6.

In vitro studies suggest that alectinib and M4 inhibit P-gp and BCRP. Alectinib did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, or OCT2 transport activity in vitro.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with alectinib have not been conducted.

Alectinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay, but was positive with an increased number of micronuclei in a rat bone marrow micronucleus test. The mechanism of micronucleus induction was abnormal chromosome segregation (aneugenicity) and not a clastogenic effect on chromosomes.

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

14 CLINICAL STUDIES

14.1 Adjuvant Treatment of Resected ALK-Positive NSCLC

The efficacy of ALECENSA for the adjuvant treatment of patients with ALK-positive NSCLC following complete tumor resection was evaluated in a global, randomized open-label clinical trial (ALINA: NCT03456076). Eligible patients were required to have resectable ALK-positive NSCLC, Stage IB (tumors ≥ 4 cm) – IIIA per the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) Staging System, 7th Edition. ALK rearrangements were identified by a locally performed FDA-approved ALK test or by a centrally performed VENTANA ALK (D5F3) CDx assay.

Randomization was stratified by race (Asian vs. other races) and stage of disease (IB vs. II vs. IIIA). Patients were randomized (1:1) to receive ALECENSA 600 mg orally twice daily or platinum-based chemotherapy following tumor resection. Treatment with ALECENSA continued for a total of 2 years, or until disease recurrence or unacceptable toxicity. Platinum-based chemotherapy was administered intravenously for 4 cycles, with each cycle lasting 21 days, according to one of the following regimens:

- Cisplatin 75 mg/m^2 on Day 1 plus vinorelbine 25 mg/m^2 on Days 1 and 8
- Cisplatin 75 mg/m^2 on Day 1 plus gemcitabine 1250 mg/m^2 on Days 1 and 8
- Cisplatin 75 mg/m^2 on Day 1 plus pemetrexed 500 mg/m^2 on Day 1

In the event of intolerance to a cisplatin-based regimen, carboplatin was administered instead of cisplatin in the above combinations at a dose of AUC 5 mg/mL/min or 6 mg/mL/min.

The major efficacy outcome measures were disease-free survival (DFS) in patients with stage II-IIIA NSCLC and DFS in patients with stage IB-IIIA NSCLC (intent-to-treat [ITT] population) as assessed by investigator. DFS was defined as the time from date of randomization to the date of occurrence of any of the following: first documented recurrence of disease, new primary NSCLC, or death due to any cause, whichever occurred first. An additional efficacy outcome measure was overall survival (OS) in the ITT population.

A total of 257 patients were randomized to ALECENSA (N=130) or to chemotherapy (N=127). The median age was 56 years (range: 26 to 87), 24% were ≥ 65 years old; 52% were female; 56% were Asian, 42% were White, 0.4% were Black or African American, 2.3% were race unknown; 0.4% were Hispanic or Latino; 60% were never smokers; 53% had an ECOG PS of 0; 10% of patients had Stage IB, 35% had Stage II and 55% had Stage IIIA disease.

ALINA demonstrated a statistically significant improvement in DFS for patients treated with ALECENSA compared to patients treated with chemotherapy. OS data were not mature at the time of DFS analysis with 2.3% of deaths reported in the ITT population.

The efficacy results from ALINA are summarized in Table 10 and Figure 1.

Table 10: Investigator-Assessed DFS Results in ALINA

Efficacy Parameter	Stage II-IIIA Population		ITT Population	
	ALECENSA N=116	Chemotherapy N=115	ALECENSA N=130	Chemotherapy N=127
DFS events (%)	14 (12)	45 (39)	15 (12)	50 (39)
Disease recurrence (%)	14 (12)	44 (38)	15 (12)	49 (38)
Death	0	1 (0.9)	0	1 (0.8)
Median DFS, months (95% CI)[a]	NR (NE, NE)	44.4 (27.8, NE)	NR (NE, NE)	41.3 (28.5, NE)
Hazard Ratio (95% CI)[b]	0.24 (0.13, 0.45)		0.24 (0.13, 0.43)	
p-value[c]	<0.0001		<0.0001	

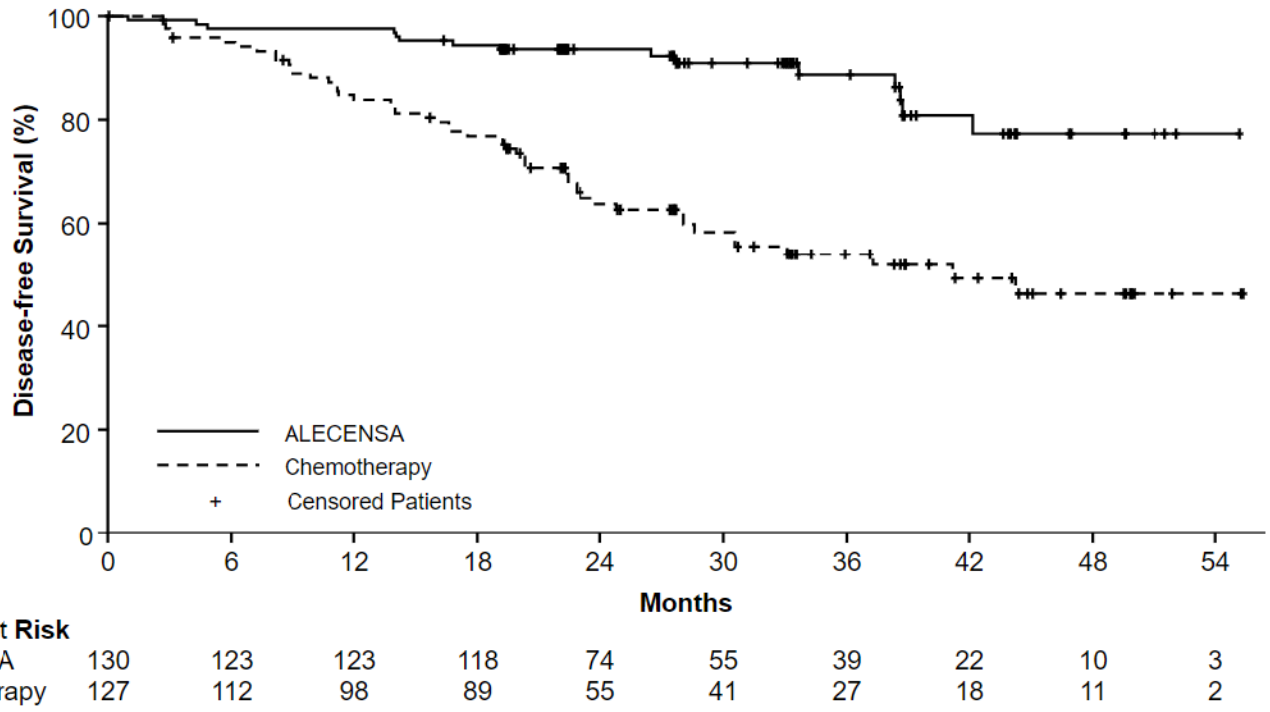
DFS = Disease-Free Survival; ITT = Intent-to-Treat; CI = Confidence Interval; NR = Not Reached; NE = Not Estimable.

[a] Kaplan-Meier method.

[b] Stratified Cox model, stratified by race (Asian vs. other races) in Stage II-IIIA and stratified by race (Asian vs. other races) and tumor stage (Stage IB vs. II vs. IIIA) in ITT.

[c] Stratified log-rank test stratified by race (Asian vs. other races) in Stage II-IIIA and stratified by race (Asian vs. other races) and tumor stage (Stage IB vs. II vs. IIIA) in ITT.

Figure 1: Kaplan-Meier Curves of Investigator-Assessed DFS (ITT Population) in ALINA



Patients at Risk

ALECENSA	130	123	123	118	74	55	39	22	10	3
Chemotherapy	127	112	98	89	55	41	27	18	11	2

In an exploratory analysis of site(s) of relapse, the proportion of patients with brain involvement at the time of disease recurrence was 4 patients (3.1%) in the ALECENSA arm and 14 patients (11%) in the chemotherapy arm.

14.2 Treatment of Metastatic ALK-Positive NSCLC

Previously Untreated Metastatic ALK-Positive NSCLC

The efficacy of ALECENSA for the treatment of patients with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease was established in an open-label, randomized, active-controlled, multicenter study (ALEX: NCT02075840). Patients were required to have an ECOG performance status of 0-2 and ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx assay. Neurologically stable patients with treated or untreated central nervous system (CNS) metastases, including leptomeningeal metastases, were eligible; patients with neurologic signs and symptoms due to CNS metastases were required to have completed whole brain radiation or gamma knife irradiation at least 14 days prior to enrollment and be clinically stable. Patients with a baseline QTc > 470 ms were ineligible.

Patients were randomized 1:1 to receive ALECENSA 600 mg orally twice daily or crizotinib 250 mg orally twice daily. Randomization was stratified by ECOG performance status (0/1 vs. 2), race (Asian vs. other races), and the presence or absence of CNS metastases at baseline. Treatment on both arms was continued until disease progression or unacceptable toxicity. The major efficacy outcome measure was progression-free survival (PFS) as determined by investigator assessment according to RECIST v1.1. Additional efficacy outcome measures were PFS as determined by independent review committee (IRC), time to CNS progression by IRC based on RECIST v1.1, objective response rate (ORR) and duration of response (DOR), and OS. Additional exploratory outcome measures were CNS objective response rate (CNS-ORR) and CNS duration of response (CNS-DOR) by IRC in patients with CNS metastases at baseline.

A total of 303 patients were randomized to ALECENSA (n=152) or crizotinib (n=151). The demographic characteristics of the study population were 56% female, median age 56 years (range: 18 to 91 years), 50% White, 46% Asian, 1% Black, and 3% other races. The majority of patients had adenocarcinoma (92%) and never smoked (63%). CNS metastases were present in 40% (n=122) of patients: of these, 43 patients had measurable CNS lesions as determined by an IRC. The ALEX study demonstrated a significant improvement in PFS. The time to cause-specific CNS progression as assessed by IRC was also significantly improved; there was a lower incidence of progression in the CNS as the first site of disease progression, alone or with concurrent systemic progression, in the ALECENSA arm (12%) as compared to the crizotinib arm (45%). Efficacy results from ALEX are summarized in Table 11 and Figure 2.

Table 11: Efficacy Results in ALEX per IRC Assessment

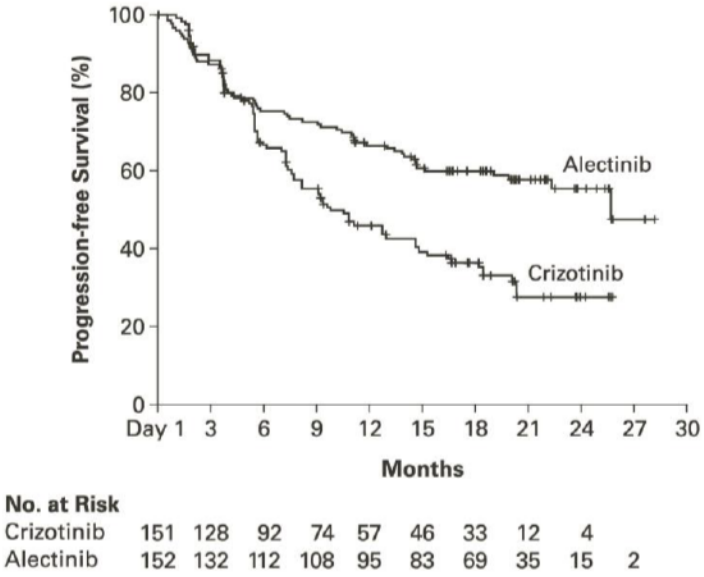
	ALECENSA N=152	**Crizotinib N=151**
Progression-Free Survival		
Number of events (%)	63 (41%)	92 (61%)
Progressive disease (%)	51 (34%)	82 (54%)
Death (%)	12 (8%)	10 (7%)
Median in months (95% CI)	25.7 (19.9, NE)	10.4 (7.7, 14.6)
Hazard ratio (95% CI) [a]	0.53 (0.38, 0.73)	
P-value [b]	< 0.0001	
Overall Response Rate		
Overall response rate, % (95% CI) [c]	79% (72, 85)	72% (64, 79)
P-value [d]	0.1652	
Complete response, %	13%	6%
Partial response, %	66%	66%
Duration of Response		
Number of responders	n=120	n=109
Response duration ≥6 months	82%	57%
Response duration ≥12 months	64%	36%
Response duration ≥18 months	37%	14%

CNS: central nervous system, ORR: overall response rate, IRC: independent review committee, CI: confidence interval, NE: not estimable.

[a, b, d] Stratified by race (Asian vs. other races) and CNS metastases at baseline (yes vs. no) for Cox model, log-rank test and Cochran Mantel-Haenszel test, respectively.

[c] Clopper and Pearson exact binomial 95% confidence interval.

Figure 2: Kaplan-Meier Plot of Progression-Free Survival (IRC) in ALEX



Results for PFS as determined by investigator assessment (HR=0.48 [95% CI: 0.35-0.66], stratified log-rank p<0.0001) were similar to that observed by IRC. At the data cutoff point overall survival data was not mature.

The results of prespecified exploratory analyses of CNS response rate in patients with measurable CNS lesions at baseline are summarized in Table 12.

Table 12: IRC-Assessed CNS Responses in Patients with Measurable CNS Lesions at Baseline in ALEX

	ALECENSA	**Crizotinib**
CNS Tumor Response Assessment	N = 21	N = 22
CNS Objective Response Rate, % (95% CI[a])	81% (58, 95)	50% (28,72)
Complete Response	38%	5%
Duration of CNS Response		
Number of responders	17	11
CNS response duration ≥ 12 months	59%	36%

IRC: Independent Review Committee; CI: Confidence Interval; NE: Not Estimable
[a] Clopper and Pearson exact binomial 95% confidence interval

Metastatic ALK-Positive NSCLC Previously Treated with Crizotinib

The safety and efficacy of ALECENSA were established in two single-arm, multicenter clinical trials: NP28761 (NCT01588028) and NP28673 (NCT01801111). Patients with locally advanced or metastatic ALK-positive NSCLC, who have progressed on crizotinib, with documented ALK-positive NSCLC based on an FDA-approved test, and ECOG PS of 0-2 were enrolled in both studies. Eligibility criteria permitted enrollment of patients with prior chemotherapy and prior CNS radiotherapy provided that CNS metastases were stable for at least two weeks. All patients received ALECENSA 600 mg orally twice daily. The major efficacy outcome measure in both studies was objective response rate (ORR) according to Response Evaluation Criteria in Solid

Tumors (RECIST v1.1) as evaluated per Independent Review Committee (IRC). Additional outcome measures as evaluated by the IRC included duration of response (DOR), CNS ORR, and CNS DOR.

NP28761 was conducted in North America and enrolled 87 patients. Baseline demographic and disease characteristics in NP28761 were median age 54 years old (range 29 to 79, 18% 65 and over), 84% White and 8% Asian, 55% female, 35% ECOG PS 0 and 55% ECOG PS 1, 100% never or former smokers, 99% Stage IV, 94% adenocarcinoma, and 74% prior chemotherapy. The most common sites of extra-thoracic metastasis included 60% CNS (of whom 65% had received CNS radiation), 43% lymph nodes, 36% bone, and 34% liver.

NP28673 was conducted internationally and enrolled 138 patients. Baseline demographic and disease characteristics in NP28673 were median age 52 years old (range 22 to 79, 10% 65 and over), 67% White and 26% Asian, 56% female, 32% ECOG PS 0 and 59% ECOG PS 1, 98% never or former smokers, 99% Stage IV, 96% adenocarcinoma, and 80% prior chemotherapy. The most common sites of extra-thoracic metastasis included 61% CNS (of whom 73% had received CNS radiation), 51% bone, 38% lymph nodes, and 30% liver.

Efficacy results from NP28761 and NP28673 in all treated patients are summarized in Table 13. The median duration of follow-up on Study NP28761 was 4.8 months for both IRC and Investigator assessments and on Study NP28673, 10.9 months for IRC assessment and 7.0 months for Investigator assessment. All responses were partial responses.

Table 13: Efficacy Results in Studies NP28761 and NP28673

Efficacy Parameter	**NP28761 (N=87)**		**NP28673 (N=138)**	
	IRC* Assessment	**Investigator Assessment**	**IRC* Assessment**	**Investigator Assessment**
Objective Response Rate (95% CI)	38% (28; 49)	46% (35; 57)	44% (36; 53)	48% (39; 57)
Number of Responders	33	40	61	66
Duration of Response, median in months (95% CI)	7.5 (4.9, Not Estimable)	NE (4.9, Not Estimable)	11.2 (9.6, Not Estimable)	7.8 (7.4, 9.2)

* 18 patients in NP28761 and 16 patients in NP28673 did not have measurable disease at baseline as per IRC assessment and were classified as non-responders in the IRC analysis.

An assessment of ORR and duration of response for CNS metastases in the subgroup of 51 patients in NP28761 and NP28673 with baseline measurable lesions in the CNS according to RECIST v1.1 are summarized in Table 14. Thirty-five (69%) patients with measurable CNS lesions had received prior brain radiation, including 25 (49%) who completed radiation treatment at least 6 months before starting treatment with ALECENSA. Responses were observed irrespective of prior brain radiation status.

Table 14: CNS Objective Response in Patients with Measurable CNS Lesions in Studies NP28761 and NP28673

Efficacy Parameter	N=51
CNS Objective Response Rate (95% CI)	61% (46, 74)
Complete Response	18%
Partial Response	43%
CNS Duration of Response, median in months (95% CI)	9.1 (5.8, Not Estimable)

16 HOW SUPPLIED/STORAGE AND HANDLING

Hard capsules, white 150 mg capsules with "ALE" printed in black ink on the cap and "150 mg" printed in black ink on the body, available in:

240 capsules per bottle: NDC 50242-130-01

Storage and stability: Do not store above 30°C (86°F). Store in the original container to protect from light and moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform patients of the following:

Hepatotoxicity

Inform patients of the signs and symptoms of bilirubin and hepatic transaminase elevations. Advise patients to contact their healthcare provider immediately for signs or symptoms of bilirubin and hepatic transaminase elevations *[see Warnings and Precautions (5.1)]*.

Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the risks of severe ILD/pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms *[see Warnings and Precautions (5.2)]*.

Renal Impairment

Inform patients of the risk of severe and potentially fatal renal impairment. Advise patients to contact their healthcare provider for change in urine color, reduced urine output, or swelling in the legs and feet *[see Warnings and Precautions (5.3)]*.

Bradycardia

Inform patients that symptoms of bradycardia including dizziness, lightheadedness, and syncope can occur while taking ALECENSA. 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 *[see Warnings and Precautions (5.4)]*.

Severe Myalgia/CPK Elevation

Inform patients of signs and symptoms of myalgia, including unexplained and/or persistent muscle pain, tenderness, or weakness. Advise patients to contact their healthcare provider immediately to report new or worsening symptoms of muscle pain or weakness *[see Warnings and Precautions (5.5)]*.

Hemolytic Anemia

Advise patients to contact their healthcare provider if they develop any signs or symptoms of hemolytic anemia *[see Warnings and Precautions (5.6)]*.

Photosensitivity

Inform patients of the signs and symptoms of photosensitivity. Advise patients to avoid prolonged sun exposure while taking ALECENSA and for at least 7 days after study drug discontinuation and to use proper protection from the sun. Advise patients to use a broad spectrum ultraviolet A (UVA)/ultraviolet B (UVB) sunscreen and lip balm (SPF $\geq$ 50) to help protect against potential sunburn *[see Adverse Reactions (6.1)]*.

Embryo-Fetal Toxicity

ALECENSA can cause fetal harm if taken during pregnancy. Advise a pregnant woman and females of reproductive potential of the potential risk to a fetus *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraception during treatment with ALECENSA and for 5 weeks after the last dose of ALECENSA. Advise patients to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.1, 8.3)]*.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ALECENSA and for 3 months after the last dose *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)]*.

Lactation

Advise women not to breastfeed during treatment with ALECENSA and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Administration

Instruct patients to take ALECENSA twice a day. Advise patients to take ALECENSA with food and to swallow ALECENSA capsules whole *[see Dosage and Administration (2.2)]*.

Missed Dose

Advise patients that if a dose of ALECENSA is missed or if the patient vomits after taking a dose of ALECENSA, patients should be advised not to take an extra dose, but to take the next dose at the regular time *[see Dosage and Administration (2.2)]*.

Distributed by:
Genentech USA, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

ALECENSA® is a registered trademark of Chugai Pharmaceutical Co., Ltd., Tokyo, Japan
©2024 Genentech, Inc. All rights reserved.

PATIENT INFORMATION

ALECENSA® (a-le-sen-sah)

(alectinib)

capsules

What is the most important information I should know about ALECENSA?

ALECENSA may cause serious side effects, including:

- **Liver problems (hepatotoxicity).** Liver problems are common with ALECENSA and can be severe. Your healthcare provider will do blood tests at least every 2 weeks for the first 3 months, and then 1 time each month and as needed during treatment with ALECENSA to check your liver function. **Tell your healthcare provider right away if you get any of the following signs and symptoms:**
  - feeling tired
  - feeling less hungry than usual
  - yellowing of your skin or the whites of your eyes
  - dark urine
  - itchy skin
  - nausea or vomiting
  - pain on the right side of your stomach area
  - bleeding or bruising more easily than normal
- **Lung problems.** ALECENSA may cause severe or life-threatening swelling (inflammation) of the lungs during treatment. Symptoms may be similar to those symptoms from lung cancer. Tell your healthcare provider right away if you have any new or worsening symptoms, including trouble breathing, shortness of breath, cough, or fever.
- **Kidney problems.** ALECENSA may cause severe kidney problems that can lead to death. Tell your healthcare provider right away if you have a change in the amount or color of your urine, or if you get new or worsening swelling in your legs or feet.
- **Slow heartbeat (bradycardia).** ALECENSA may cause very slow heartbeats that can be severe. Your healthcare provider will check your heart rate and blood pressure during treatment with ALECENSA. Tell your healthcare provider right away if you feel dizzy, lightheaded, or if you faint during treatment with ALECENSA. Tell your healthcare provider if you take any heart or blood pressure medicines.
- **Severe muscle pain, tenderness, and weakness (myalgia).** Muscle problems are common with ALECENSA and can be severe. Your healthcare provider will do blood tests at least every 2 weeks for the first month and as needed during treatment with ALECENSA. Tell your healthcare provider 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.
- **Breakdown of healthy red blood cells earlier than normal (hemolytic anemia).** Hemolytic anemia can happen in some people who take ALECENSA. If this happens, you may not have enough healthy red blood cells. Your healthcare provider may temporarily stop ALECENSA and do blood tests, if needed, to check for this problem. If you develop hemolytic anemia, your healthcare provider may either restart you on ALECENSA at a lower dose when the hemolytic anemia goes away, or may stop your treatment with ALECENSA. Tell your healthcare provider right away if you experience yellow skin (jaundice), weakness or dizziness, or shortness of breath.

See "What are the possible side effects of ALECENSA?" for more information about side effects.

What is ALECENSA?

ALECENSA is a prescription medicine used to treat adults with non-small cell lung cancer (NSCLC) that is caused by an abnormal anaplastic lymphoma kinase (ALK) gene:

- to help prevent your lung cancer from coming back after your tumor has been removed by surgery (adjuvant), **or**
- as treatment when your lung cancer has spread to other parts of your body (metastatic).

Your healthcare provider will perform a test to make sure that ALECENSA is right for you.

It is not known if ALECENSA is safe and effective in children.

Before you take ALECENSA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems
- have lung or breathing problems
- have a slow heartbeat
- are pregnant or plan to become pregnant. ALECENSA can harm your unborn baby.

  Females who are able to become pregnant:
  - Your healthcare provider will do a test to see if you are pregnant before starting treatment with ALECENSA.
  - You should use effective birth control (contraception) during treatment with ALECENSA and for 5 weeks after the last dose of ALECENSA.
  - Tell your healthcare provider right away if you become pregnant during treatment with ALECENSA or think you may be pregnant.

  Males who have female partners that are able to become pregnant should use effective birth control (contraception) during treatment with ALECENSA and for 3 months after the last dose of ALECENSA.
- are breastfeeding or plan to breastfeed. It is not known if ALECENSA passes into your breast milk. Do not breastfeed during treatment with ALECENSA and for 1 week after the last dose of ALECENSA. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, or herbal supplements.

How should I take ALECENSA?

- Take ALECENSA exactly as your healthcare provider tells you to take it. Do not change your dose or stop taking ALECENSA unless your healthcare provider tells you to.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with ALECENSA if you have side effects.
- Take ALECENSA 2 times a day.
- Take ALECENSA with food.
- Swallow ALECENSA capsules whole. Do not open or dissolve the capsule contents.
- If you miss a dose of ALECENSA, do not take the missed dose. Take your next dose at your regular time.
- If you vomit after taking a dose of ALECENSA, do not take an extra dose. Take your next dose at your regular time.

What should I avoid while taking ALECENSA?

Avoid spending time in the sunlight during treatment with ALECENSA and for 7 days after the last dose of ALECENSA. Your skin may be sensitive to the sun (photosensitivity) and you may burn more easily and get severe sunburns. Use sun protecting measures, such as sunscreen and lip balm with an SPF 50 or greater to help protect against sunburn.

What are the possible side effects of ALECENSA?

ALECENSA may cause serious side effects, including:

- **See "What is the most important information I should know about ALECENSA?"**

The most common side effects of ALECENSA include:

- constipation
- tiredness
- swelling in your hands, feet, ankles, face and eyelids
- rash
- cough

These are not all of the possible side effects of ALECENSA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ALECENSA?

- Do not store ALECENSA at temperatures above 86°F (30°C).
- Store ALECENSA capsules in the original container.
- Keep ALECENSA capsules dry and away from light.

Keep ALECENSA and all medicines out of the reach of children.

General information about the safe and effective use of ALECENSA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ALECENSA for a condition for which it was not prescribed. Do not give ALECENSA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ALECENSA that is written for health professionals.

What are the ingredients in ALECENSA?

Active ingredient: alectinib

Inactive ingredients: lactose monohydrate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate and carboxymethylcellulose calcium. Capsule shell contains: hypromellose, carrageenan, potassium chloride, titanium dioxide, corn starch, and carnauba wax. Printing ink contains: red iron oxide (E172), yellow iron oxide (E172), FD&C Blue No. 2 aluminum lake (E132), carnauba wax, white shellac, and glyceryl monooleate.

Distributed by: Genentech, Inc., A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990

ALECENSA® is a registered trademark of Chugai Pharmaceutical Co., Ltd., Tokyo, Japan

© 2024 Genentech, Inc.

For more information, go to www.ALECENSA.com or call 1-800-253-2367.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 04/2024

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Alecensa 150 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains alectinib hydrochloride equivalent to 150 mg alectinib.

Excipients with known effect
Each hard capsule contains 33.7 mg lactose (as monohydrate) and 6 mg sodium (as sodium laurilsulfate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

White hard capsule of 19.2 mm length, with "ALE" printed in black ink on the cap and "150 mg" printed in black ink on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adjuvant treatment of resected non-small cell lung cancer (NSCLC)

Alecensa as monotherapy is indicated as adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence (see section 5.1 for selection criteria).

Treatment of advanced NSCLC

Alecensa as monotherapy is indicated for the first-line treatment of adult patients with ALK-positive advanced NSCLC.

Alecensa as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.

4.2 Posology and method of administration

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

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

Posology
The recommended dose of Alecensa is 600 mg (four 150 mg capsules) taken twice daily with food (total daily dose of 1200 mg).

Patients with underlying severe hepatic impairment (Child-Pugh C) should receive a starting dose of 450 mg taken twice daily with food (total daily dose of 900 mg).

Duration of treatment

Adjuvant treatment of resected NSCLC
Treatment with Alecensa should be continued until disease recurrence, unacceptable toxicity or for 2 years.

Treatment of advanced NSCLC
Treatment with Alecensa should be continued until disease progression or unacceptable 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. Patients should not take two doses at the same time to make up for a missed dose. If vomiting occurs after taking a dose of Alecensa, patients should take the next dose at the scheduled time.

Dose adjustments
Management of adverse events may require dose reduction, temporary interruption, 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.

Dose modification advice is provided in Tables 1 and 2 below.

Table 1 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

Table 2 Dose modification advice for specified adverse drug reactions (see sections 4.4 and 4.8)

CTCAE grade	Alecensa treatment
ILD/pneumonitis of any severity grade	Immediately interrupt and permanently discontinue Alecensa if no other potential causes of ILD/pneumonitis have been identified.
ALT or AST elevation of > 5 times ULN with total bilirubin ≤ 2 times ULN	Temporarily withhold until recovery to baseline or ≤ 3 times ULN, then resume at reduced dose (see Table 1).
ALT or AST elevation of > 3 times ULN with total bilirubin elevation > 2 times ULN in the absence of cholestasis or haemolysis	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 ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. Evaluate concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products. If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. If no contributing concomitant medicinal product is identified, or if contributing concomitant medicinal products are not discontinued or dose

CTCAE grade	Alecensa treatment
	modified, resume at reduced dose (see Table 1) 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 if no contributing concomitant medicinal product is identified. If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at reduced dose (see Table 1) 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 the 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 1.
Haemolytic anaemia with haemoglobin of < 10 g/dL (Grade ≥ 2)	Temporarily withhold until resolution, then resume at reduced dose (see Table 1).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; CTCAE = NCI Common Terminology Criteria for Adverse Events; ILD = interstitial lung disease; ULN = upper limit of normal

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

Special populations

Hepatic impairment

No starting dose adjustment is required in patients with underlying mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Patients with underlying severe hepatic impairment (Child-Pugh C) should receive a starting dose of 450 mg taken twice daily (total dose of 900 mg) (see section 5.2). For all patients with hepatic impairment, appropriate monitoring (e.g. markers of liver function) is advised, see section 4.4.

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 section 5.2).

Elderly (≥ 65 years)

The limited data on the safety and efficacy of Alecensa in patients aged 65 years and older do not suggest that a dose adjustment is required in elderly patients (see section 5.2). There are no available data on patients over 80 years of age.

Paediatric population

The safety and efficacy of Alecensa in children and adolescents below 18 years of age have not been established. No data are available.

Extreme body weight (> 130 kg)
Although pharmacokinetic (PK) simulations for Alecensa do not indicate a low exposure in patients with extreme body weight (i.e. >130 kg), alectinib is widely distributed and clinical studies for alectinib enrolled patients within a range of body weights of 36.9–123 kg. There are no available data on patients with body weight above 130 kg.

Method of administration
Alecensa is for oral use. The hard capsules should be swallowed whole, and must not be opened or dissolved. They must be taken with food (see section 5.2).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Interstitial lung disease (ILD)/pneumonitis
Cases of ILD/pneumonitis have been reported in clinical trials with Alecensa (see section 4.8). 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 4.2).

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 4.8). 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 3 times the ULN and total bilirubin greater than or equal 2 times the ULN, with normal alkaline phosphatase, occurred in one 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. Thereafter, monitoring should be performed periodically, since events may occur later than 3 months, with more frequent testing in patients who develop aminotransferase and bilirubin elevations. Based on the severity of the adverse drug reaction, Alecensa should be withheld and resumed at a reduced dose, or permanently discontinued as described in Table 2 (see section 4.2).

Severe myalgia and creatine phosphokinase (CPK) elevation
Myalgia or musculoskeletal pain was reported in patients in pivotal trials with Alecensa, including Grade 3 events (see section 4.8).

Elevations of CPK occurred in pivotal trials with Alecensa, including Grade 3 events (see section 4.8). Median time to Grade ≥ 3 CPK elevation was 15 days across clinical trials (BO40336, BO28984, NP28761, NP28673).

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, Alecensa should be withheld, then resumed or dose reduced (see section 4.2).

Bradycardia
Symptomatic bradycardia can occur with Alecensa (see section 4.8). Heart rate and blood pressure should be monitored as clinically indicated. Dose modification is not required in case of asymptomatic bradycardia (see section 4.2). If patients experience symptomatic bradycardia or life-threatening events, concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products should be evaluated and Alecensa treatment should be adjusted as described in Table 2 (see sections 4.2 and 4.5, 'P-gp substrates' and 'BCRP substrates').

Haemolytic anaemia
Haemolytic anaemia has been reported with Alecensa (see section 4.8). If haemoglobin concentration is below 10 g/dL and haemolytic anaemia is suspected, Alecensa should be withheld and appropriate laboratory testing should be initiated. If haemolytic anaemia is confirmed, Alecensa should be resumed at a reduced dose upon resolution as described in Table 2 (see section 4.2).

Gastrointestinal perforation
Cases of gastrointestinal perforations have been reported in patients at increased risk (e.g., history of diverticulitis, metastases to the gastrointestinal tract, concomitant use of medicinal product with a recognised risk of gastrointestinal perforation) treated with alectinib. Discontinuation of Alecensa in patients who develop gastrointestinal perforation should be considered. Patients should be informed of the signs and symptoms of gastrointestinal perforations and advised to consult rapidly in case of occurrence.

Photosensitivity
Photosensitivity to sunlight has been reported with Alecensa administration (see section 4.8). 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) sunscreen and lip balm (sun protection factor [SPF] ≥50) to help protect against potential sunburn.

Embryo-foetal toxicity
Alecensa may cause foetal harm when administered to a pregnant woman. Female patients of childbearing potential receiving Alecensa, must use highly effective contraceptive methods during treatment and for at least 5 weeks following the last dose of Alecensa (see sections 4.5, 4.6 and 5.3). Male patients with female partners of childbearing potential must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of Alecensa (see sections 4.6 and 5.3).

Lactose intolerance
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, a congenital lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium content
This medicinal product contains 48 mg sodium per daily dose (1200 mg), equivalent to 2.4 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products 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 total hepatic metabolism. M4 has shown similar *in vitro* potency and activity 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 reduced alectinib C_{max}, and AUC_{inf} by 51 % and 73 % respectively and increased M4 C_{max}-and AUC_{inf} 2.20 and 1.79-fold respectively. The effect on the

combined exposure of alectinib and M4 was minor, reducing C_{max} and AUC_{inf} by 4 % and 18 %, respectively. Based on the effects on the combined exposure of alectinib and M4, no dose adjustments are required when Alecensa is co-administered with CYP3A inducers. Appropriate monitoring is recommended for patients taking concomitant strong CYP3A inducers (including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort (Hypericum perforatum)).

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 increased alectinib exposure C_{max} and AUC_{inf} by 1.18 and 1.75-fold respectively, and reduced M4 C_{max} and AUC_{inf} by 71 % and 25 % respectively. The effect on the combined exposure of alectinib and M4 was minor, reducing C_{max} by 7 % and increasing AUC_{inf} 1.36-fold. Based on the effects on the combined exposure of alectinib and M4, no dose adjustments are required when Alecensa is co-administered with CYP3A inhibitors. Appropriate monitoring is recommended for patients taking concomitant strong CYP3A inhibitors (including, but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole nefazodone, grapefruit or Seville oranges).

Medicinal products that increase gastric pH
Multiple doses of esomeprazole, a proton pump inhibitor, 40 mg once daily, 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 medicinal products which raise gastric pH (e.g. H2 receptor antagonists or antacids).

Effect of transporters on alectinib disposition
M4 is a substrate of P-glycoprotein (P-gp). As alectinib inhibits P-gp, it is not expected that co-medication with P-gp inhibitors has a relevant effect on M4 exposure.

Effects of alectinib on other medicinal products

CYP substrates
In vitro, alectinib and M4 show weak time-dependent inhibition of CYP3A4, and alectinib exhibits a weak induction potential of CYP3A4 and CYP2B6 at clinical concentrations.

Multiple doses of 600 mg alectinib had no influence on the exposure of midazolam (2 mg), a sensitive CYP3A substrate. Therefore, no dose adjustment is required for co-administered CYP3A substrates. A risk for induction of CYP2B6 and pregnane X receptor (PXR) regulated enzymes apart from CYP3A4 cannot be completely excluded. The effectiveness of concomitant administration of oral contraceptives may be reduced.

P-gp substrates
In vitro, alectinib and its major active metabolite M4 are inhibitors of the efflux transporter P-gp. Therefore, alectinib and M4 may have the potential to increase plasma concentrations of co-administered substrates of P-gp. When Alecensa is co-administered with P-gp substrates (e.g., digoxin, dabigatran etexilate, topotecan, sirolimus, everolimus, nilotinib and lapatinib), appropriate monitoring is recommended.

Breast cancer resistance protein (BCRP) substrates
In vitro, alectinib and M4 are inhibitors of the efflux transporter BCRP. Therefore, alectinib and M4 may have the potential to increase plasma concentrations of co-administered substrates of BCRP. When Alecensa is co-administered with BCRP substrates (e.g., methotrexate, mitoxantrone, topotecan and lapatinib), appropriate monitoring is recommended.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential must be advised to avoid pregnancy while on Alecensa (see section 4.4).

Contraception in female patients
Female patients of childbearing potential receiving Alecensa must use highly effective contraceptive methods during treatment and for at least 5 weeks following the last dose of Alecensa (see sections 4.4 and 4.5).

Contraception in male patients
Male patients with female partners of childbearing potential must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of Alecensa (see section 4.4).

Pregnancy
There are no or limited amount of data from the use of alectinib in pregnant women. Based on its mechanism of action, alectinib may cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity (see section 5.3).

Female patients who become pregnant while taking Alecensa or during the 5 weeks following the last dose of Alecensa must contact their doctor and should be advised of the potential harm to the foetus.

Male patients with female partners who become pregnant while the male patient is taking Alecensa, or during the 3 months following the last dose of Alecensa, must contact their doctor, and their female partner should seek medical advice due to the potential harm to the foetus based on its aneugenic potential (see section 5.3).

Breast-feeding
It is unknown whether alectinib and/or its metabolites are excreted in human milk. A risk to the newborn/infant cannot be excluded. Mothers should be advised against breast-feeding while receiving Alecensa.

Fertility
No fertility studies in animals have been performed to evaluate the effect of alectinib. No adverse effects on male and female reproductive organs were observed in general toxicology studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Alecensa has minor influence on the ability to drive and use machines. Caution should be exercised when driving or operating machines as patients may experience symptomatic bradycardia (e.g., syncope, dizziness, hypotension) or vision disorders while taking Alecensa (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The data described below reflect exposure to Alecensa in 533 patients with resected or advanced ALK-positive NSCLC. These patients received Alecensa at the recommended dose of 600 mg twice daily in pivotal clinical trials for adjuvant treatment of resected NSCLC (BO40336, ALINA) or for treatment of advanced NSCLC (BO28984, ALEX; NP28761; NP28673). See section 5.1 for further information on clinical trial participants.

In BO40336 (ALINA; N = 128), the median duration of exposure to Alecensa was 23.9 months. In BO28984 (ALEX; N = 152) the median duration of exposure to Alecensa was 28.1 months. In the

phase II clinical trials (NP28761, NP28673; N = 253), the median duration of exposure to Alecensa was 11.2 months.
The most common adverse drug reactions (ADRs) (≥ 20 %) were constipation, myalgia, oedema, increased bilirubin, increased AST, anaemia, rash and increased ALT.

Tabulated list of adverse drug reactions
Table 3 lists the ADRs occurring in patients who received Alecensa across clinical trials (BO40336, BO28984, NP28761, NP28673).

The ADRs listed in Table 3 are presented by system organ class and frequency categories, defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000). Within each system organ class, undesirable effects are presented in order of decreasing frequency and severity. Within the same frequency and severity grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3 ADRs reported in Alecensa clinical trials (BO40336, BO28984, NP28761, NP28673; N = 533)

System organ class ADRs (MedDRA)	**Alecensa** **N = 533**	
	Frequency category (all grades)	**Frequency category (grades 3-4)**
Blood and lymphatic system disorders		
Anaemia[1)]	Very common	Common
Haemolytic anaemia[2)]	Common	-*
Nervous system disorders		
Dysgeusia[3)]	Common	Uncommon
Eye disorders		
Vision disorders[4)]	Common	-*
Cardiac disorders		
Bradycardia[5)]	Very common	-*
Respiratory, thoracic and mediastinal disorders		
Interstitial lung disease / pneumonitis	Common	Uncommon
Gastrointestinal disorders		
Diarrhoea	Very common	Common
Vomiting	Very common	Uncommon
Constipation	Very common	Uncommon
Nausea	Very common	Uncommon
Stomatitis[6)]	Common	Uncommon
Hepatobiliary disorders		
Increased AST	Very common	Common
Increased ALT	Very common	Common
Increased bilirubin[7)]	Very common	Common
Increased alkaline phosphatase	Very Common	Uncommon
Drug-induced liver injury[8)]	Uncommon	Uncommon
Skin and subcutaneous tissue disorders		
Rash[9)]	Very common	Common
Photosensitivity	Common	Uncommon

System organ class ADRs (MedDRA)	Alecensa N = 533	
	Frequency category (all grades)	**Frequency category (grades 3-4)**
Musculoskeletal and connective tissues disorders		
Myalgia[10)]	Very common	Uncommon
Increased blood creatine phosphokinase	Very common	Common
Renal and urinary disorders		
Blood creatinine increased	Very common	Uncommon**
Acute kidney injury	Common	Uncommon**
General disorders and administration site conditions		
Oedema[11)]	Very common	Uncommon
Investigations		
Weight increased	Very common	Uncommon
Metabolism and Nutrition Disorders		
Hyperuricaemia[12)]	Common	-*

*No Grade 3-4 ADRs were observed.
**Includes one Grade 5 event (observed in the advanced NSCLC setting).
[1)] includes cases of anaemia, haemoglobin decreased and normochromic normocytic anaemia.
[2)] cases reported in study BO40336 (N = 128).
[3)] includes cases of dysgeusia, hypogeusia, and taste disorder.
[4)] includes cases of blurred vision, visual impairment, vitreous floaters, reduced visual acuity, asthenopia, diplopia, photophobia, and photopsia.
[5)] includes cases of bradycardia and sinus bradycardia.
[6)] includes cases of stomatitis and mouth ulceration.
[7)] includes cases of blood bilirubin increased, hyperbilirubinaemia, bilirubin conjugated increased, and blood bilirubin unconjugated increased.
[8)] includes two patients 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.
[9)] includes cases of rash, rash maculopapular, dermatitis, dermatitis acneiform, erythema, rash papular, rash pruritic, rash macular, exfoliative rash, and rash erythematous.
[10)] includes cases of myalgia, musculoskeletal pain, and arthralgia.
[11)] includes cases of oedema peripheral, oedema, generalised oedema, eyelid oedema, periorbital oedema, face oedema, localised oedema, peripheral swelling, face swelling, lip swelling, swelling, joint swelling and eyelid swelling.
[12)] includes cases of hyperuricaemia and increased blood uric acid.

Description of selected adverse drug reactions

Interstitial lung disease (ILD) / pneumonitis

Across clinical trials, ILD/pneumonitis occurred in 1.7 % of patients treated with Alecensa. 0.4 % of these cases were Grade 3 and treatment discontinuations due to ILD/pneumonitis occurred in 1.1 % of patients, and in 0.4 % of patients, the event led to dose modifications. In the phase III clinical trial BO28984, Grade 3 or 4 ILD/pneumonitis was not observed in patients receiving Alecensa versus 2.0 % of patients receiving crizotinib. There were no fatal cases of ILD in any of the clinical trials. Patients should be monitored for pulmonary symptoms indicative of pneumonitis (see sections 4.2 and 4.4).

Hepatotoxicity

Across clinical trials, three patients had a documented drug-induced liver injury (including two patients with the reported term drug-induced liver injury and one patient with reported Grade 4 increased AST and ALT who had documented drug-induced liver injury by liver biopsy). Adverse reactions of increased AST and ALT levels (23.6 % and 20.5 % respectively) were reported in patients treated with Alecensa across clinical trials. The majority of these events were of Grade 1 and 2 intensity, and events of Grade $\geq$ 3 were reported in 3.0 % and 3.2 % of the patients for increased AST and ALT levels, 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

2.3 % and 3.6 % of the patients, respectively) or dose reduction (1.7 % and 1.5 %, respectively). In 1.3 % and 1.5 % of the patients, AST and ALT elevations, respectively, led to withdrawal from Alecensa treatment. Grade 3 or 4 ALT or AST elevations were observed in 4.6 % and 5.3 % of patients receiving Alecensa versus 16.6 % and 10.6 % of patients receiving crizotinib in the phase III clinical trial BO28984.

Adverse reactions of bilirubin elevations were reported in 25.9 % of the patients treated with Alecensa across clinical trials. The majority of the events were of Grade 1 and 2 intensity; Grade ≥ 3 events were reported in 3.9 % of the patients. The events generally occurred during the first 3 months of treatment, were usually transient and the majority resolved upon dose modification. In 8.3 % of patients, bilirubin elevations led to dose modifications and in 2.1 % of patients, bilirubin elevations led to withdrawal from Alecensa treatment. In the phase III clinical trial BO28984, Grade 3 or 4 bilirubin elevations occurred in 5.9 % of patients receiving Alecensa versus no patient receiving crizotinib.

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 one patient (0.2 %) treated in Alecensa clinical trials.

Patients should be monitored for liver function including ALT, AST, and total bilirubin as outlined in section 4.4 and managed as recommended in section 4.2.

Bradycardia
Cases of bradycardia (11.3 %) of Grade 1 or 2 have been reported in patients treated with Alecensa across clinical trials. No patients had events of Grade ≥ 3 severity. There were 102 of 521 patients (19.6 %) treated with Alecensa, for whom serial ECGs were available, had post-dose heart rate values below 50 beats per minute (bpm). In the phase III clinical trial BO28984 12.4 % of patients treated with Alecensa had post-dose heart rate values below 50 bpm versus 17.6 % of patients treated with crizotinib. Patients who develop symptomatic bradycardia should be managed as recommended in sections 4.2 and 4.4. No case of bradycardia led to withdrawal from Alecensa treatment.

Severe myalgia and CPK elevations
Cases of myalgia (35.3 %) including myalgia events (24.2 %), arthralgia (16.3 %), and musculoskeletal pain (0.8 %) have been reported in patients treated with Alecensa across clinical trials. The majority of events were Grades 1 or 2 and five patients (0.9 %) had a Grade 3 event. Dose modifications of Alecensa treatment due to these adverse events were required for nine patients (1.7 %); Alecensa treatment was not withdrawn due to these events of myalgia. Elevations of CPK occurred in 56.2 % of 491 patients with CPK laboratory data available across clinical trials with Alecensa. The incidence of Grade ≥ 3 elevations of CPK was 5.5 %. Median time to Grade ≥ 3 CPK elevation was 15 days across trials. Dose modifications for elevation of CPK occurred in 5.4 % of patients; withdrawal from Alecensa treatment did not occur due to CPK elevations. In the clinical trial BO28984, severe arthralgia was reported in one patient (0.7 %) in the alectinib arm and in two patients (1.3 %) in the crizotinib arm. Grade ≥ 3 elevation of CPK was reported for 3.3 % of patients receiving Alecensa and 4.6 % of patients receiving crizotinib.

Haemolytic anaemia
Haemolytic anaemia has been observed in 3.1 % of patients treated with Alecensa in the clinical trial setting. These cases were Grade 1 or 2 (non-serious) and did not lead to treatment discontinuation (see sections 4.2 and 4.4).

Gastrointestinal effects
Constipation (39.6 %), diarrhoea (18.8 %), nausea (17.6 %), and vomiting (12.4 %) were the most commonly reported gastrointestinal (GI) reactions. Most of these events were of mild or moderate severity; Grade 3 events were reported for diarrhoea (1.1 %), nausea (0.4 %), constipation (0.4 %), and vomiting (0.2 %). These events did not lead to withdrawal from Alecensa treatment. Median time to onset for constipation, nausea, diarrhoea, and/or vomiting events across clinical trials was 21 days. The events declined in frequency after the first month of treatment. In the phase III clinical trial BO28984, Grade 3 and 4 events of nausea and constipation were reported in one patient each (0.7 %),

while diarrhoea was reported in 2 patients (1.3 %) in the alectinib arm; the incidence of Grade 3 and 4 events of nausea, vomiting and diarrhoea was 3.3 %, 3.3 % and 2.0 %, respectively, in the crizotinib arm.

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

4.9 Overdose

Patients who experience overdose should be closely supervised and general supportive care instituted. There is no specific antidote for overdose with Alecensa.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-neoplastic agents, protein kinase inhibitor; ATC code: L01ED03.

Mechanism of action

Alectinib is a highly selective and potent ALK and rearranged during transfection (RET) tyrosine kinase inhibitor. In pre-clinical studies, inhibition of ALK tyrosine kinase activity led to blockage of downstream signalling pathways including signal transducer and activator of transcription 3 (STAT 3) and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and induction of 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.
Based on preclinical data, alectinib is not a substrate of P-gp or 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.

Clinical efficacy and safety

Adjuvant treatment of resected ALK-positive NSCLC

The efficacy of Alecensa for the adjuvant treatment of patients with ALK-positive NSCLC following complete tumour resection was established in a global randomised Phase III open-label clinical trial (BO40336; ALINA). Eligible patients were required to have Stage IB (tumours ≥ 4 cm) - Stage IIIA NSCLC per the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) Staging System, 7th Edition, with ALK-positive disease identified by a locally performed CE-marked ALK test, or centrally performed by the Ventana ALK (D5F3) immunohistochemistry (IHC) assay.

The following selection criteria define patients with high risk of recurrence who are included in the therapeutic indication and are reflective of the patient population with Stage IB (tumours ≥ 4 cm) – IIIA NSCLC according to the 7th Edition UICC/AJCC staging criteria:

Tumour size ≥ 4 cm; or tumours of any size that are either accompanied by N1 or N2 status; or tumours that are invasive of thoracic structures (directly invade the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve the

main bronchus < 2 cm distal to the carina but without involvement of the carina; or tumours that are associated with atelectasis or obstructive pneumonitis of the entire lung; or tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary.

The study did not include patients who had N2 status with tumours also invading the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, or with separate tumour nodule(s) in a different ipsilateral lobe.

Patients were randomised (1:1) to receive Alecensa or platinum-based chemotherapy following tumour resection. Randomisation was stratified by race (Asian and non-Asian) and stage of disease (IB, II and IIIA). Alecensa was administered at the recommended oral dose of 600 mg twice daily for a total of 2 years, or until disease recurrence or unacceptable toxicity. Platinum-based chemotherapy was administered intravenously for 4 cycles, with each cycle lasting 21 days, according to one of the following regimens:

Cisplatin 75 mg/m^2 on Day 1 plus vinorelbine 25 mg/m^2 on Days 1 and 8
Cisplatin 75 mg/m^2 on Day 1 plus gemcitabine 1250 mg/m^2 on Days 1 and 8
Cisplatin 75 mg/m^2 on Day 1 plus pemetrexed 500 mg/m^2 on Day 1

In the event of intolerance to a cisplatin-based regimen, carboplatin was administered instead of cisplatin in the above combinations at a dose of area under the free carboplatin plasma versus time curve (AUC) 5 mg/mL/min or AUC 6 mg/mL/min.

The primary efficacy endpoint was disease-free survival (DFS) as assessed by the Investigator. DFS was defined as the time from date of randomisation to the date of occurrence of any of the following: first documented recurrence of disease, new primary NSCLC, or death due to any cause, whichever occurred first. The secondary and exploratory efficacy endpoints were overall survival (OS) and time to CNS recurrence or death (CNS-DFS).

A total of 257 patients were studied: 130 patients were randomised to the Alecensa arm, and 127 patients were randomised to the chemotherapy arm. Overall, the median age was 56 years (range: 26 to 87), and 24 % were ≥ 65 years old, 52 % were female, 56 % were Asian, 60 % were never smokers, 53 % had an ECOG PS of 0, 10 % of patients had Stage IB, 36 % had Stage II and 54 % had Stage IIIA disease.

ALINA demonstrated a statistically significant improvement in DFS for patients treated with Alecensa compared to patients treated with chemotherapy in the Stage II-IIIA and the Stage IB (≥ 4 cm) - IIIA (ITT) patient populations. OS data were not mature at the time of DFS analysis with 2.3 % of deaths reported overall. The median duration of survival follow-up was 27.8 months in the Alecensa arm and 28.4 months in the chemotherapy arm.

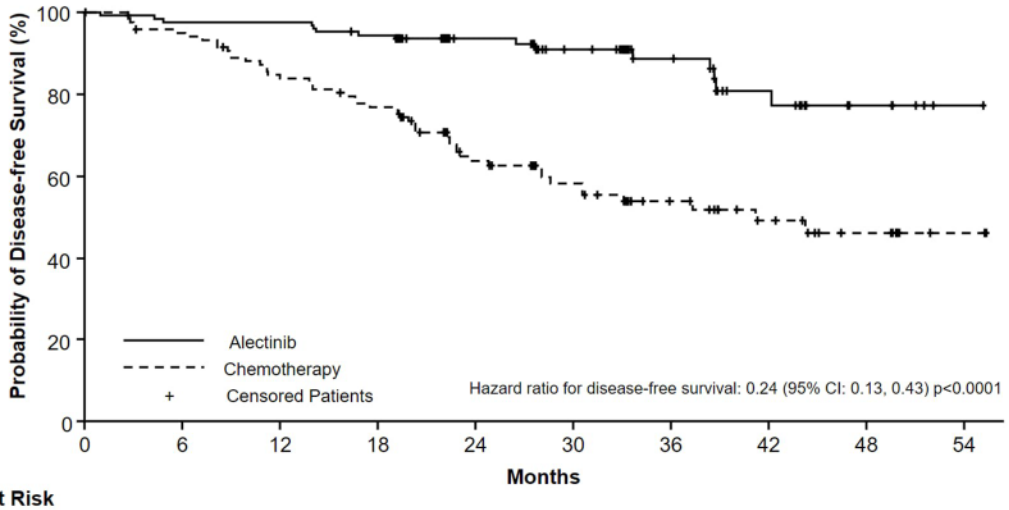
The DFS efficacy results are summarised in Table 4 and Figure 1.

Table 4 Investigator assessed DFS results in ALINA

Efficacy Parameter	Stage II-IIIA		ITT Population	
	Alecensa n = 116	Chemotherapy n = 115	Alecensa n = 130	Chemotherapy n = 127
Number of DFS events (%)	14 (12.1)	45 (39.1)	15 (11.5)	50 (39.4)
Median DFS, months (95 % CI)	NE (NE, NE)	44.4 (27.8, NE)	NE (NE, NE)	41.3 (28.5, NE)
Stratified HR (95 % CI)*	0.24 (0.13, 0.45)		0.24 (0.13, 0.43)	
p-value (log-rank)*	< 0.0001		< 0.0001	

DFS = Disease-Free Survival; ITT = Intent-to-Treat; CI = Confidence Interval; NE = Not Estimable; HR = Hazard Ratio
*Stratified by race in Stage II-IIIA, stratified by race and stage in Stage IB-IIIA.

Figure 1: Kaplan-Meier curve of investigator assessed DFS in the ITT population



Patients at Risk

Alectinib	130	123	123	118	74	55	39	22	10	3
Chemotherapy	127	112	98	89	55	41	27	18	11	2

Treatment of advanced ALK-positive NSCLC

Treatment-naïve patients

The safety and efficacy of Alecensa were studied in a global randomised Phase III open label clinical trial (BO28984, ALEX) 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 was required before randomisation into the study.

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

Eastern Cooperative Oncology Group performance status ((ECOG PS) (0/1 vs. 2)), race (Asian vs. non-Asian), and central nervous system (CNS) metastases at baseline (yes vs. no) were stratification factors for randomisation. 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 Response Evaluation Criteria in Solid Tumors (RECIST) version 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).

The trial met its primary endpoint at the primary analysis, demonstrating a statistically significant improvement in PFS by investigator. Efficacy data are summarised in Table 5 and the Kaplan-Meier curve for investigator assessed PFS is shown in Figure 2. Additionally, the Kaplan-Meier plot of overall survival from the final OS analysis is presented in Figure 3.

Table 5 Summary of efficacy results from study BO28984 (ALEX)

	Crizotinib n = 151	**Alecensa n = 152**
Median duration of follow-up (months) ‡	23.3 (range 0.3 – 123.5)	53.5(range 0.5 – 126.8)
Primary efficacy parameter		
PFS (INV) †		
Number of patients with event n (%)	102 (68 %)	62 (41 %)
Median (months)	11.1	NE
[95 % CI]	[9.1; 13.1]	[17.7; NE]
HR	0.47	
[95 % CI]	[0.34, 0.65]	
Stratified log-rank p-value	p < 0.0001	
Secondary efficacy parameters		
PFS (IRC)*, †		
Number of patients with event n (%)	92 (61 %)	63 (41 %)
Median (months)	10.4	25.7
[95 % CI]	[7.7; 14.6]	[19.9; NE]
HR	0.50	
[95 % CI]	[0.36; 0.70]	
Stratified log-rank p-value	p < 0.0001	
Time to CNS progression (IRC)*, **, †		
Number of patients with event n (%)	68 (45 %)	18 (12 %)
Cause-specific HR	0.16	
[95 % CI]	[0.10; 0.28]	
Stratified log-rank p-value	p < 0.0001	
12-month cumulative incidence of CNS progression (IRC)	41.4 %	9.4 %
[95 % CI]	[33.2; 49.4]	[5.4; 14.7]
ORR (INV)*, ***, †		
Responders n (%)	114 (75.5 %)	126 (82.9 %)
[95 % CI]	[67.8; 82.1]	[76.0; 88.5]
Overall survival*, ‡		
Number of patients with event n (%)	73 (48.3 %)	76 (50.0 %)
Median (months)	54.2	81.1
[95 % CI]	[34.6; 75.6]	[62.3; NE]

	Crizotinib n = 151	**Alecensa n = 152**
HR [95 % CI]	0.78 [0.56; 1.08]	
Duration of response (INV) ‡ Median (months) [95 % CI]	n = 115 11.1 [7.9; 13.0]	n = 126 42.3 [31.3; 51.3]
CNS-ORR in patients with measurable CNS metastases at baseline† 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]

* 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

† Data from primary analysis

‡ Data from final OS analysis, which was conducted after 149 deaths had occurred.

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 PFS benefit was consistent for patients with CNS metastases at baseline (hazard ratio (HR) = 0.40, 95 % confidence interval (CI): 0.25-0.64, median PFS for Alecensa = not estimable (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 2: Kaplan Meier plot of INV assessed PFS in BO28984 (ALEX)

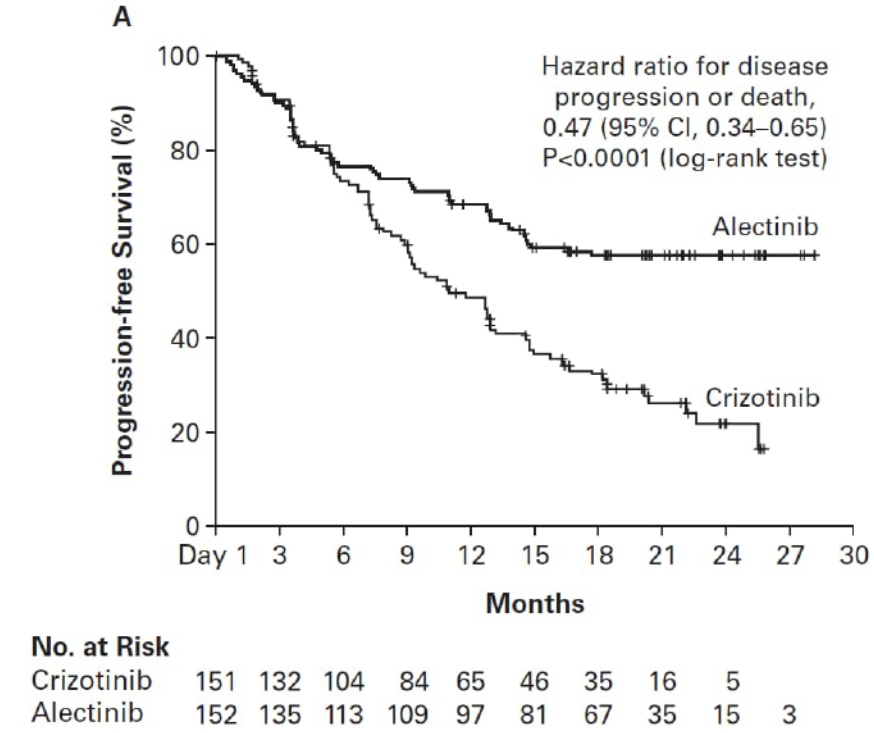
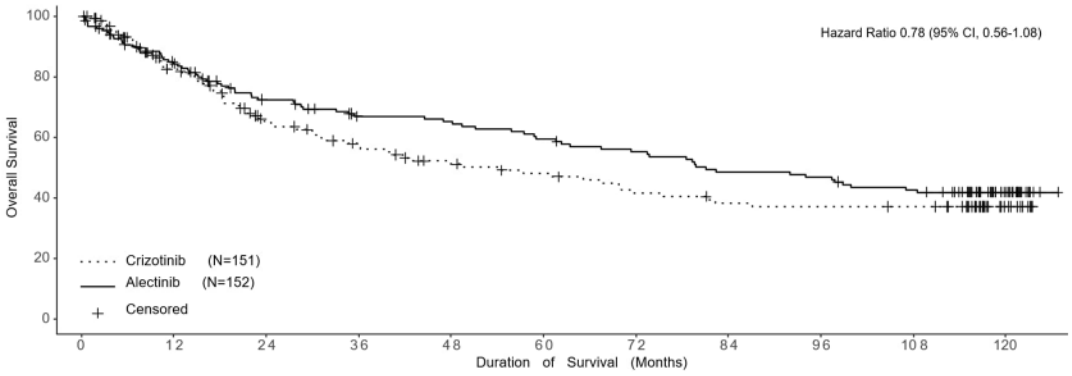


Figure 3: Kaplan Meier plot of overall survival in BO28984 (ALEX)



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 (NP28673 and NP28761).

NP28673
Study NP28673 was a Phase I/II single arm, multicentre 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 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 Objective Response Rate (ORR) as per central Independent Review Committee (IRC) assessment using RECIST version 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. A lower confidence limit for the estimated ORR above the pre-specified threshold of 35 % would achieve a statistically significant result.

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 PS at baseline was 0 or 1 in 90.6 % of patients and 2 in 9.4 % 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 tumours were classified as adenocarcinoma. Among patients included in the study, 20 % of the patients had previously progressed on crizotinib treatment only, and 80 % had previously progressed on crizotinib and at least one chemotherapy treatment.

Study NP28761
Study NP28761 was a Phase I/II single arm multicentre 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 ORR as per central IRC assessment using RECIST version 1.1. A lower confidence limit for the estimated ORR above the pre-specified threshold of 35 % would achieve a statistically significant result.

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. The median age was 54 years. The majority of patients had no history of smoking (62 %). The ECOG PS at baseline was 0 or 1 in 89.7 % of patients and 2 in 10.3 % of patients. At the time of entry in the study, 99 % of patients had stage IV disease, 60 % had brain metastases and in 94 % of patients tumours were classified as adenocarcinoma. Among the patients included in the study, 26 % of the patients had previously progressed on crizotinib treatment only, and 74 % had previously progressed on crizotinib and at least one chemotherapy treatment.

The main efficacy results from studies NP28673 and NP28761 are summarised in Table 6. A summary of pooled analysis of CNS endpoints is presented in Table 7.

Table 6 Efficacy results from studies NP28673 and NP28761

	NP28673 Alecensa 600 mg twice daily	**NP28761 Alecensa 600 mg twice daily**
Median duration of follow-up (months)	21 (range 1 – 30)	17 (range 1 – 29)
Primary efficacy parameters		
ORR (IRC) in RE population Responders n (%) [95 % CI]	n = 122 [a] 62 (50.8 %) [41.6 %, 60.0 %]	n = 67 [b] 35 (52.2 %) [39.7 %, 64.6 %]
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]	n = 35 20 (57.1 %) 14.9 [6.9, NE]
PFS (IRC) Number of patients with events n (%) Median duration (months) [95 % CI]	n = 138 98 (71.0 %) 8.9 [5.6, 12.8]	n = 87 58 (66.7 %) 8.2 [6.3, 12.6]

CI = confidence interval; DOR = duration of response; 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] 20 patients did not have measurable disease at baseline according to the IRC and were not included in the IRC response evaluable population

ORR results for studies NP28673 and NP28761 were consistent across subgroups of baseline patient characteristics such as age, gender, race, ECOG PS, CNS metastasis and prior chemotherapy use, especially when considering the small number of patients in some subgroups.

Table 7 Summary of the pooled analysis of CNS endpoints from studies NP28673 and NP28761

CNS Parameters (NP28673 and NP28761)	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 DOR (IRC)	n = 32
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; ORR = objective response rate; NE = not estimable

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

5.2 Pharmacokinetic properties

The pharmacokinetic parameters for alectinib and its major active metabolite (M4) have been characterised in ALK-positive NSCLC patients and healthy subjects. Based on population pharmacokinetic analysis, the geometric mean (coefficient of variation %) steady-state C_{max}, C_{min} and $AUC_{0\text{-}12hr}$ 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 $AUC_{0\text{-}12hr}$ for M4 were approximately 246 ng/mL (45.4 %), 222 ng/mL (46.6 %) and 2810 ng*h/mL (45.9 %), respectively.

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

Alectinib steady-state is reached within 7 days with continuous 600 mg twice daily dosing. The accumulation ratio for the twice-daily 600 mg regimen was approximately 6-fold. 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 capsules 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, alectinib and M4 exposure was increased by around 3-fold relative to fasted conditions (see section 4.2).

Distribution
Alectinib and its major metabolite M4 are highly bound to human plasma proteins (> 99 %), independent of active substance 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 intravenous administration was 475 L, indicating extensive distribution into tissues.
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.

Biotransformation
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. Results from the human mass balance study demonstrated that alectinib and M4 were the main circulating moieties in plasma with 76 % of the total radioactivity in plasma. The geometric mean Metabolite/Parent ratio at steady state is 0.399.

Metabolite M1b was detected as a minor metabolite from *in vitro* and in human plasma in healthy subjects. Formation of metabolite M1b and its minor isomer M1a is likely to be catalysed by a combination of CYP isozymes (including isozymes other than CYP3A) and aldehyde dehydrogenase (ALDH) enzymes.

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 did not inhibit OATP1B1/OATP1B3, OAT1, OAT3 or OCT2 at clinically relevant concentrations in vitro.

Elimination
Following administration of a single dose of ^{14}C-labeled alectinib administered orally to healthy subjects the majority of radioactivity was excreted in faeces (mean recovery 97.8 %) with minimal excretion in urine (mean recovery 0.46 %). In faeces, 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.

Pharmacokinetics in special populations

Renal impairment
Negligible amounts of alectinib and the active metabolite M4 are excreted unchanged in urine (< 0.2 % of the dose). Based on a population pharmacokinetic analysis alectinib and M4 exposures were similar in patients with mild and moderate renal impairment and normal renal function. The pharmacokinetics of alectinib has not been studied in patients with severe 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 metabolite M4. Based on a population pharmacokinetic analysis, alectinib and M4 exposures were similar in patients with mild hepatic impairment and normal hepatic function.

Following administration of a single oral dose of 300 mg alectinib in subjects with severe (Child-Pugh C) hepatic impairment, alectinib C_{max} was the same and AUC_{inf} was 2.2-fold higher compared with the same parameters in matched healthy subjects. M4 C_{max} and AUC_{inf} was 39 % and 34 % lower respectively, resulting in a combined exposure of alectinib and M4 (AUC_{inf}) 1.8-fold higher in patients with severe hepatic impairment compared with matched healthy subjects.

The hepatic impairment study also included a group with moderate (Child-Pugh B) hepatic impairment, and a modestly higher alectinib exposure was observed in this group compared with matched healthy subjects. The subjects in the Child Pugh B group however did in general not suffer from abnormal bilirubin, albumin or prothrombin time, indicating that they may not be fully representative of moderately hepatically impaired subjects with decreased metabolic capacity.

Effects of age, body weight, race and gender
Age, body weight, race and gender had no clinically meaningful effect on the systemic exposure of alectinib and M4. The range of body weights for patients enrolled in clinical studies is 36.9-123 kg. There are no available data on patients with extreme body weight (>130 kg) (see section 4.2).

5.3 Preclinical safety data

Carcinogenicity
Carcinogenicity studies have not been performed to establish the carcinogenic potential of alectinib.

Mutagenicity
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 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.

Impairment of fertility
No fertility studies in animals have been performed to evaluate the effect of alectinib. No adverse effects on male and female reproductive organs were observed in general toxicology studies. These studies were 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 area under the curve (AUC), at the recommended dose of 600 mg twice daily.

Teratogenicity
Alectinib caused embryo-foetal toxicity in pregnant rats and rabbits. In pregnant rats, alectinib caused total embryo-foetal loss (miscarriage) at exposures 4.5-fold of the human AUC exposure and small foetuses with retarded ossification and minor abnormalities of the organs at exposures 2.7-fold of the human AUC exposure. In pregnant rabbits, alectinib caused embryo-foetal loss, small foetuses and increased incidence of skeletal variations at exposures 2.9-fold of the human AUC exposure at the recommended dose.

Other
Alectinib absorbs ultraviolet (UV) light between 200 and 400 nm and demonstrated a 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 gastrointestinal (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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Lactose monohydrate
Hydroxypropylcellulose
Sodium laurilsulfate
Magnesium stearate
Carmellose calcium

Capsule shell
Hypromellose
Carrageenan
Potassium chloride
Titanium dioxide (E171)
Maize starch
Carnauba wax

Printing ink
Red iron oxide (E172)
Yellow iron oxide (E172)
Indigo carmine aluminum lake (E132)
Carnauba wax
White shellac
Glyceryl monooleate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Blisters
Store in the original package in order to protect from moisture.

Bottles
Store in the original package and keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/aluminium (PA/Alu/PVC/Alu) blisters containing 8 hard capsules.
Pack size: 224 (4 packs of 56) hard capsules.

HDPE bottle with a child-resistant closure and an integrated desiccant.
Pack size: 240 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1169/001
EU/1/16/1169/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 February 2017
Date of latest renewal: 15 July 2022

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release
Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

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

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

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreeed subsequent updates of the RMP.

An updated RMP should be submitted:

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

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

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

Description	Due Date
Post Authorisation Efficacy Study (PAES): In order to further evaluate the efficacy of Alecensa as monotherapy as adjuvant treatment following complete tumour resection for adult patients with Stage IB (≥ 4 cm) - IIIA ALK-positive NSCLC, the MAH should submit the following results from the BO40336 study:	
• Updated descriptive DFS and descriptive OS results	Q3 2025
• 5-year survival follow up results	Q3 2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Alecensa 150 mg hard capsules
alectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains alectinib hydrochloride equivalent to 150 mg alectinib.

3. LIST OF EXCIPIENTS

Contains lactose and sodium. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

224 (4 packs of 56) hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1169/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

alecensa

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Alecensa 150 mg hard capsules
alectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains alectinib hydrochloride equivalent to 150 mg alectinib.

3. LIST OF EXCIPIENTS

Contains lactose and sodium. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

56 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1169/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

alecensa

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Alecensa 150 mg hard capsules
alectinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Alecensa 150 mg hard capsules
alectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains alectinib hydrochloride equivalent to 150 mg alectinib.

3. LIST OF EXCIPIENTS

Contains lactose and sodium. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

240 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package and keep the bottle tightly closed in order to protect from moisture

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1169/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

alecensa

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Alecensa 150 mg hard capsules
alectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains alectinib hydrochloride equivalent to 150 mg alectinib.

3. LIST OF EXCIPIENTS

Contains lactose and sodium. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

240 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package and keep the bottle tightly closed in order to protect from moisture

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1169/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Alecensa 150 mg hard capsules
alectinib

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

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

What is in this leaflet

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

1. What Alecensa is and what it is used for

What Alecensa is

Alecensa is a cancer medicine that contains the active substance alectinib.

What Alecensa is used for

Alecensa is used to treat adults with a type of lung cancer called 'non-small cell lung cancer' ('NSCLC') that is 'ALK-positive' - this means your cancer cells have a fault in a gene that makes an enzyme called ALK ('anaplastic lymphoma kinase') fusion, see 'How Alecensa works', below.

Alecensa can be prescribed to you:
- after removal of your cancer as a post-surgical (adjuvant) treatment, or
- as the first treatment of your lung cancer that has spread to other parts of the body (advanced), or if you have been previously treated with a medicine containing 'crizotinib'.

How Alecensa works

Alecensa blocks the action of an enzyme called 'ALK tyrosine kinase'. Abnormal forms of this enzyme (due to fault in the gene that makes it) help encourage cancer cell growth. Alecensa may slow down or stop the growth of your cancer and may prevent the tumour from coming back after removal by surgery. It may also help to shrink your cancer.

If you have any questions about how Alecensa works or why this medicine has been prescribed for you, ask your doctor, pharmacist or nurse.

2. What you need to know before you take Alecensa

Do not take Alecensa

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

If you are not sure, talk to your doctor, pharmacist or nurse before taking Alecensa.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Alecensa:
- if you have ever had stomach or intestine problems as holes (perforation), or if you have conditions causing inflammation inside the abdomen (diverticulitis), or if you have spread of cancer inside the abdomen (metastasis). It is possible that Alecensa may increase the risk of developing holes in the wall of your gut.
- if you have an inherited problem called 'galactose intolerance', 'congenital lactase deficiency' or 'glucose-galactose malabsorption'.

If you are not sure, talk to your doctor, pharmacist or nurse before taking Alecensa.

Talk to your doctor right away after having taken Alecensa:
- if you are experiencing severe stomach or abdominal pain, fever, chills, sickness, vomiting, or abdominal rigidity or bloating, as these could be symptoms of a hole in the wall of your gut.

Alecensa can cause side effects that you need to tell your doctor about straight away. These include:
- liver injury (hepatotoxicity). Your doctor will take blood tests before you start treatment, then every 2 weeks for the first 3 months of your treatment and then less often. This is to check you do not have any liver problems while taking Alecensa. Tell your doctor straight away if you get any of the following signs: yellowing of your skin or the whites of your eyes, pain on the right side of your stomach area, dark urine, itchy skin, feeling less hungry than usual, nausea or vomiting, feeling tired, bleeding or bruising more easily than normal.
- slow heart beat (bradycardia).
- lung inflammation (pneumonitis). Alecensa may cause severe or life-threatening swelling (inflammation) of the lungs during treatment. The signs may be similar to those from your lung cancer. Tell your doctor straight away if you have any new or worsening signs including difficulty in breathing, shortness of breath, or cough with or without mucus, or fever.
- severe muscle pain, tenderness, and weakness (myalgia). Your doctor will do blood tests at least every 2 weeks for the first month and as needed during treatment with Alecensa. Tell your doctor straight away if you get new or worsening signs of muscle problems, including unexplained muscle pain or muscle pain that does not go away, tenderness, or weakness.
- abnormal breakdown of red blood cells (haemolytic anaemia). Tell your doctor straight away if you feel tired, weak or short of breath.

Look out for these while you are taking Alecensa. See 'Side effects' in section 4 for more information.

Sensitivity to sunlight

Do not expose yourself to the sun for any long period of time while you are taking Alecensa and for 7 days after you stop. You need to apply sunscreen and lip balm with a sun protection factor (SPF) of 50 or higher to help prevent sunburn.

Tests and checks

When you take Alecensa your doctor will do blood tests before you start treatment, then every 2 weeks for the first 3 months of your treatment and then less often. This is to check you do not have any liver or muscle problems while taking Alecensa.

Children and adolescents

Alecensa has not been studied in children or adolescents. Do not give this medicine to children or adolescents under the age of 18 years.

Other medicines and Alecensa

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, and herbal medicines. This is because Alecensa can affect the way some other medicines work. Also some other medicines can affect the way Alecensa works.

In particular tell your doctor or pharmacist if you are taking any of the following medicines:
- digoxin, a medicine used to treat heart problems
- dabigatran etexilate, a medicine used to treat blood clots
- methotrexate, a medicine used to treat severe joint inflammation, cancer and the skin disease psoriasis
- nilotinib, a medicine used to treat certain types of cancer
- lapatinib, a medicine used to treat certain types of breast cancer
- mitoxantrone, a medicine used to treat certain types of cancer or multiple sclerosis (a disease that affects the central nervous system which damages the coating that protects the nerves)
- everolimus, a medicine used to treat certain types of cancer or used to prevent the body's immune system from rejecting an organ transplant
- sirolimus, a medicine used to prevent the body's immune system from rejecting an organ transplant
- topotecan, a medicine used to treat certain types of cancer
- medicines used to treat acquired immunodeficiency syndrome/human immunodeficiency virus (AIDS/HIV) (e.g. ritonavir, saquinavir)
- medicines used to treat infections. These include medicines that treat fungal infections (antifungals such as ketoconazole, itraconazole, voriconazole, posaconazole) and medicines that treat certain types of bacterial infection (antibiotics such as telithromycin)
- St. John's Wort, a herbal medicine used to treat depression
- medicines used to stop seizures or fits (anti-epileptics such as phenytoin, carbamazepine, or phenobarbital)
- medicines used to treat tuberculosis (e.g. rifampicin, rifabutin)
- nefazodone, a medicine used to treat depression

Oral contraceptives

If you take Alecensa whilst using oral contraceptives, the oral contraceptives may be less effective.

Alecensa with food and drink

Tell your doctor or pharmacist if you drink grapefruit juice or eat grapefruit or Seville oranges while on treatment with Alecensa as they may change the amount of Alecensa in your body.

Contraception, pregnancy, and breast-feeding

Contraception - information for women

- You should not become pregnant while taking this medicine. If you are able to become pregnant, you must use highly effective contraception while on treatment and for at least 5 weeks after stopping treatment. If you take Alecensa whilst using oral contraceptives, the oral contraceptives may be less effective.

Contraception - information for men

- You should not father a child while taking this medicine. If your female partner is able to become pregnant, you must use highly effective contraception while on treatment and for at least 3 months after stopping treatment.

Talk to your doctor about the right methods of contraception for you and your partner.

Pregnancy

- Do not take Alecensa if you are pregnant. This is because it may harm your baby.
- If you become pregnant while taking the medicine or during the 5 weeks after taking your last dose, tell your doctor straight away.
- If your female partner becomes pregnant while you are taking the medicine or during the 3 months after taking your last dose, tell your doctor straight away, and your female partner should seek medical advice.

Breast-feeding

- Do not breast-feed while taking this medicine. This is because it is not known if Alecensa can pass over into breast milk and could therefore harm your baby.

Driving and using machines

Take special care when driving and using machines as you may develop problems with vision or slowing of the heartbeat or low blood pressure that can lead to fainting or dizziness while you are taking Alecensa.

Alecensa contains lactose

Alecensa contains lactose (a type of sugar). If you have been told by your doctor that you cannot tolerate or digest some sugars, talk to your doctor before taking this medicine.

Alecensa contains sodium

This medicine contains 48 mg sodium (main component of cooking/table salt) per recommended daily dose (1200 mg). This is equivalent to 2.4 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take Alecensa

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

How much to take

- The recommended dose is 4 capsules (600 mg) twice a day.
- This means you take a total of 8 capsules (1200 mg) each day.

If you have severe liver problems before starting your treatment with Alecensa:

- The recommended dose is 3 capsules (450 mg) twice a day.
- This means you take a total of 6 capsules (900 mg) each day.

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

How to take

- Alecensa is taken by mouth. Swallow each capsule whole. Do not open or dissolve the capsules.
- You must take Alecensa with food.

If you vomit after taking Alecensa

If you vomit after taking a dose of Alecensa, do not take an extra dose, just take your next dose at the usual time.

If you take more Alecensa than you should

If you take more Alecensa than you should, talk to a doctor or go to hospital straight away. Take the medicine pack and this leaflet with you.

If you forget to take Alecensa

- If it is more than 6 hours until your next dose, take the missed dose as soon as you remember.
- If it is less than 6 hours until your next dose, skip the missed dose. Then take your next dose at the usual time.
- Do not take a double dose to make up for a missed dose.

If you stop taking Alecensa

Do not stop taking this medicine without talking to your doctor first. It is important to take Alecensa twice a day for as long as your doctor prescribes it for you.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine. Some side effects could be serious.

Tell your doctor straight away if you notice any of the following side effects. Your doctor may lower your dose, stop your treatment for a short time or stop your treatment completely:

- New or worsening signs including difficulty in breathing, shortness of breath, or cough with or without mucus, or fever - the signs may be similar to those from your lung cancer (potential signs of lung inflammation – pneumonitis). Alecensa can cause severe or life-threatening inflammation of the lungs during treatment.
- Yellowing of your skin or the whites of your eyes, pain on the right side of your stomach area, dark urine, itchy skin, feeling less hungry than usual, nausea or vomiting, feeling tired, bleeding or bruising more easily than normal (potential signs of liver problems)
- New or worsening signs of muscle problems, including unexplained muscle pain or muscle pain that does not go away, tenderness, or weakness (potential signs of muscle problems).
- Fainting, dizziness and low blood pressure (potential signs of slow heart beat)
- Feeling tired, weak or short of breath (potential signs of an abnormal breakdown of red blood cells, known as haemolytic anaemia).

Other side effects

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

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

- abnormal results of blood tests to check for liver problems (high levels of alanine aminotransferase, aspartate aminotransferase and bilirubin)

- abnormal results of blood tests to check for muscle damage (high level of creatine phosphokinase)
- abnormal results of blood tests to check for liver disease or bone disorders (high level of alkaline phosphatase)
- you may feel tired, weak or short of breath due to a reduction in the number of red blood cells, known as anaemia
- vomiting – if you vomit after taking a dose of Alecensa, do not take an extra dose, just take your next dose at the usual time
- constipation
- diarrhoea
- nausea
- rash
- swelling caused by fluid build-up in the body (oedema)
- weight gain
- abnormal results of blood tests to check kidney function (high level of creatinine)

Common (may affect up to 1 in 10 people):
- inflammation of the mucous membrane of the mouth
- sensitivity to sunlight – do not expose yourself to the sun for any long period of time while you are taking Alecensa and for 7 days after you stop. You need to apply sunscreen and lip balm with a Sun Protection Factor of 50 or higher to help prevent sunburn.
- alteration in sense of taste
- problem with your eyes including blurred vision, loss of sight, black dots or white spots in your vision, and seeing double
- increased levels of uric acid in the blood (hyperuricaemia)
- kidney problems including rapid loss of kidney function (acute kidney injury)

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

5. How to store Alecensa

- Keep this medicine out of the sight and reach of children.
- Do not take this medicine after the expiry date which is stated on the carton and either the blister or the bottle after EXP. The expiry date refers to the last day of that month.
- If Alecensa is packed in blisters, store in the original package in order to protect from moisture.
- If Alecensa is packed in bottles, store in the original package and keep the bottle tightly closed to protect from moisture.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Alecensa contains

- The active substance is alectinib. Each hard capsule contains alectinib hydrochloride equivalent to 150 mg alectinib.
- The other ingredients are:

- *Capsule content:* lactose monohydrate (see section 2 'Alecensa contains lactose'), hydroxypropylcellulose, sodium laurilsulfate (see section 2 'Alecensa contains sodium'), magnesium stearate and carmellose calcium
- *Capsule shell:* hypromellose, carrageenan, potassium chloride, titanium dioxide (E171), maize starch and carnauba wax
- *Printing ink:* red iron oxide (E172), yellow iron oxide (E172), indigo carmine aluminium lake (E132), carnauba wax, white shellac and glyceryl monooleate.

What Alecensa looks like and contents of the pack

Alecensa hard capsules are white, with 'ALE' printed in black ink on the cap and '150 mg' printed in black ink on the body.

The capsules are provided in blisters and are available in cartons containing 224 hard capsules (4 packs of 56). The capsules are also available in plastic bottles containing 240 hard capsules. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

Manufacturer

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien, Luxembourg/Luxemburg N.V. Roche S.A. België/Belgique/Belgien Tél/Tel: +32 (0) 2 525 82 11	**Latvija** Roche Latvija SIA Tel: +371 - 6 7039831
България Рош България ЕООД Тел: +359 2 474 5444	**Lietuva** UAB "Roche Lietuva" Tel: +370 5 2546799
Česká republika Roche s. r. o. Tel: +420 - 2 20382111	**Magyarország** Roche (Magyarország) Kft. Tel: +36 - 1 279 4500
Danmark Roche Pharmaceuticals A/S Tlf.: +45 - 36 39 99 99	**Nederland** Roche Nederland B.V. Tel: +31 (0) 348 438000

Deutschland Roche Pharma AG Tel: +49 (0) 7624 140	**Norge** Roche Norge AS Tlf: +47 - 22 78 90 00
Eesti Roche Eesti OÜ Tel: + 372 - 6 177 380	**Österreich** Roche Austria GmbH Tel: +43 (0) 1 27739
Ελλάδα, Κύπρος Roche (Hellas) A.E. Ελλάδα Τηλ: +30 210 61 66 100	**Polska** Roche Polska Sp.z o.o. Tel: +48 - 22 345 18 88
España Roche Farma S.A. Tel: +34 - 91 324 81 00	**Portugal** Roche Farmacêutica Química, Lda Tel: +351 - 21 425 70 00
France Roche Tél: +33 (0) 1 47 61 40 00	**România** Roche România S.R.L. Tel: +40 21 206 47 01
Hrvatska Roche d.o.o. Tel: +385 1 4722 333	**Slovenija** Roche farmacevtska družba d.o.o. Tel: +386 - 1 360 26 00
Ireland, Malta Roche Products (Ireland) Ltd Ireland/L-Irlanda Tel: +353 (0) 1 469 0700	**Slovenská republika** Roche Slovensko, s.r.o. Tel: +421 - 2 52638201
Ísland Roche Pharmaceuticals A/S c/o Icepharma hf Sími: +354 540 8000	**Suomi/Finland** Roche Oy Puh/Tel: +358 (0) 10 554 500
Italia Roche S.p.A. Tel: +39 - 039 2471	**Sverige** Roche AB Tel: +46 (0) 8 726 1200

This leaflet was last revised in {**MM/YYYY**}.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web-site: https://www.ema.europa.eu.

次項以降は非公表のため削除

CORE DATA SHEET [redacted]

[redacted]

ALECENSA, ALECENSARO

Alectinib

[redacted]