

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALECENSA safely and effectively. See full prescribing information for ALECENSA.

ALECENSA® (alectinib) capsules, for oral use
Initial U.S. Approval: 2015

----- **INDICATIONS AND USAGE** -----

ALECENSA is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1)

----- **DOSAGE AND ADMINISTRATION** -----

600 mg orally twice daily. Administer ALECENSA with food. (2.1)

----- **DOSAGE FORMS AND STRENGTHS** -----

Capsules: 150 mg (3)

----- **CONTRAINDICATIONS** -----

None. (4)

----- **WARNINGS AND PRECAUTIONS** -----

- Hepatotoxicity: Monitor liver laboratory tests every 2 weeks during the first 2 months of treatment, and then periodically during treatment. In case of severe ALT, AST, or bilirubin elevations, withhold, then reduce dose, or permanently discontinue ALECENSA. (2.2, 5.1)

- Interstitial Lung Disease (ILD)/Pneumonitis: Occurred in 0.4% of patients. Immediately withhold ALECENSA in patients diagnosed with ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis have been identified. (2.2, 5.2)
- Bradycardia: Monitor heart rate and blood pressure regularly. If symptomatic, withhold ALECENSA then reduce dose, or permanently discontinue. (2.2, 5.3)
- Severe Myalgia and Creatine Phosphokinase (CPK) Elevation: Occurred in 1.2% and 4.6% of patients, respectively. Assess CPK every 2 weeks during the first month of treatment and in patients reporting unexplained muscle pain, tenderness, or weakness. In case of severe CPK elevations, withhold, then resume or reduce dose. (2.2, 5.4)
- Embryo-Fetal Toxicity: ALECENSA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.5, 8.1 8.3)

----- **ADVERSE REACTIONS** -----

The most common adverse reactions (incidence $\geq 20\%$) were fatigue, constipation, edema and myalgia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **USE IN SPECIAL POPULATIONS** -----

Lactation: Do not breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2015

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1 **FULL PRESCRIBING INFORMATION**

2
3 **1 INDICATIONS AND USAGE**

4 ALECENSA is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive,
5 metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

6 This indication is approved under accelerated approval based on tumor response rate and duration of response
7 [see *Clinical Studies (14)*]. Continued approval for this indication may be contingent upon verification and
8 description of clinical benefit in a confirmatory trial.

9
10 **2 DOSAGE AND ADMINISTRATION**

11 **2.1 Dosing and Administration**

12 The recommended dose of ALECENSA is 600 mg orally twice daily with food [see *Clinical Pharmacology*
13 (12.3)]. Administer ALECENSA until disease progression or unacceptable toxicity.

14 Do not open or dissolve the contents of the capsule.

15 If a dose of ALECENSA is missed or vomiting occurs after taking a dose of ALECENSA, take the next dose at
16 the scheduled time.

17 **2.2 Dose Modifications for Adverse Reactions**

18 The dose reduction schedule for ALECENSA is provided in Table 1.

19 **Table 1. ALECENSA Dose Reduction Schedule**

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

20
21 Discontinue if patients are unable to tolerate the 300 mg twice daily dose.

22 Recommendations for dose modifications of ALECENSA in case of adverse reactions are provided in Table 2.

23 **Table 2. ALECENSA Dose Modifications for Adverse Reactions**

Criteria ^a	ALECENSA Dose Modification
ALT or AST elevation of greater than 5 times upper limit of normal (ULN) <u>with</u> total bilirubin less than or equal to 2 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 3 times ULN, then resume at reduced dose as per Table 1.
ALT or AST elevation greater than 3 times ULN <u>with</u> total bilirubin elevation greater than 2 times ULN in the absence of cholestasis or hemolysis	Permanently discontinue ALECENSA.
Total bilirubin elevation of greater than 3 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 1.5 times ULN, then resume at reduced dose as per Table 1.
Any grade treatment-related interstitial lung disease (ILD)/pneumonitis	Permanently discontinue ALECENSA.
Symptomatic bradycardia	Withhold ALECENSA until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume ALECENSA at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume ALECENSA at reduced dose (see Table 1) upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.
Bradycardia ^b (life-threatening consequences, urgent intervention indicated)	Permanently discontinue ALECENSA if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume ALECENSA at reduced dose (see Table 1) upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. Permanently discontinue ALECENSA in case of recurrence.
CPK elevation greater than 5 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at same dose.
CPK elevation greater than 10 times ULN or second occurrence of CPK elevation of greater than 5 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at reduced dose as per Table 1.

24 ^a ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal; ILD = interstitial lung
25 disease; CPK = blood creatine phosphokinase

26 ^b Heart rate less than 60 beats per minute (bpm)

27
28 **3 DOSAGE FORMS AND STRENGTHS**

29 150 mg hard capsules, white, with “ALE” printed in black ink on the cap and “150 mg” printed in black ink on
30 the body.

31

32 **4 CONTRAINDICATIONS**

33 None.

34 **5 WARNINGS AND PRECAUTIONS**

35 **5.1 Hepatotoxicity**

36 Elevations of AST greater than 5 times the upper limit of normal (ULN) occurred in 3.6% of patients, and
37 elevations of ALT greater than 5 times the ULN occurred in 4.8% of patients. Elevations of bilirubin greater
38 than 3 times the ULN occurred in 2.8% of patients. The majority (73% of the patients with hepatic transaminase
39 elevations and 49% of the patients with bilirubin elevations) of these events occurred during the first 2 months
40 of treatment. Four patients discontinued ALECENSA for Grade 3-4 AST and/or ALT elevations, and 3 patients
41 discontinued ALECENSA for Grade 3 bilirubin elevations. Two patients with Grade 3-4 AST/ALT elevations
42 had documented drug induced liver injury by liver biopsy.

43 Monitor liver function tests including ALT, AST, and total bilirubin every 2 weeks during the first 2 months of
44 treatment, then periodically during treatment, with more frequent testing in patients who develop transaminase
45 and bilirubin elevations. Based on the severity of the adverse drug reaction, withhold ALECENSA and resume
46 at a reduced dose, or permanently discontinue ALECENSA as described in Table 2 [*see Dosage and*
47 *Administration (2.2)*].

48 **5.2 Interstitial Lung Disease (ILD)/Pneumonitis**

49 Severe ILD (Grade 3) occurred in one (0.4%) of 253 patients exposed to ALECENSA in clinical trials.

50 Promptly investigate for ILD/pneumonitis in any patient who presents with worsening of respiratory symptoms
51 indicative of ILD/pneumonitis (e.g., dyspnea, cough and fever).

52 Immediately withhold ALECENSA treatment in patients diagnosed with ILD/pneumonitis and permanently
53 discontinue ALECENSA if no other potential causes of ILD/pneumonitis have been identified [*see Dosage and*
54 *Administration (2.2) and Adverse Reactions (6)*].

55 **5.3 Bradycardia**

56 Symptomatic bradycardia can occur with ALECENSA. Cases of bradycardia (7.5%) have been reported in
57 patients treated with ALECENSA. Twenty percent of 221 patients treated with ALECENSA for whom serial
58 ECGs were available had heart rates of less than 50 beats per minute (bpm).

59 Monitor heart rate and blood pressure regularly. Dose modification is not required in cases of asymptomatic
60 bradycardia. In cases of symptomatic bradycardia that is not life-threatening, withhold ALECENSA until
61 recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above and evaluate concomitant
62 medications known to cause bradycardia, as well as anti-hypertensive medications. If attributable to a
63 concomitant medication, resume ALECENSA at a reduced dose (see Table 1) upon recovery to asymptomatic
64 bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. Permanently
65 discontinue ALECENSA in case of recurrence. Permanently discontinue ALECENSA in cases of life-
66 threatening bradycardia if no contributing concomitant medication is identified [*see Dosage and Administration*
67 *(2.2)*].

68 **5.4 Severe Myalgia and Creatine Phosphokinase (CPK) Elevation**

69 Myalgia or musculoskeletal pain occurred in 29% of patients in Study 1 and Study 2. The incidence of Grade 3
70 myalgia/musculoskeletal pain was 1.2%. Dose modifications for myalgia/musculoskeletal pain were required in
71 0.8% of patients.

72 Elevations of CPK occurred in 43% of 218 patients with CPK laboratory data available in Study 1 and Study 2.
73 The incidence of Grade 3 elevations of CPK was 4.6%. Median time to Grade 3 CPK elevation was 14 days
74 (interquartile range 13-14 days). Dose modifications for elevation of CPK occurred in 5.0% of patients.

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

79 **5.5 Embryo-Fetal Toxicity**

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

85 Advise females of reproductive potential to use effective contraception during treatment with ALECENSA and
86 for 1 week following the final dose [*see Use in Specific Populations (8.1 and 8.3) and Clinical Pharmacology*
87 *(12.1)*].

88 **6 ADVERSE REACTIONS**

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

- 90 • Hepatotoxicity [*see Warnings and Precautions (5.1)*]
- 91 • Interstitial Lung Disease (ILD)/Pneumonitis [*see Warnings and Precautions (5.2)*]
- 92 • Bradycardia [*see Warnings and Precautions (5.3)*]
- 93 • Severe Myalgia and Creatine Phosphokinase (CPK) Elevation [*see Warnings and Precautions (5.4)*]
- 94 • Embryo-Fetal Toxicity [*see Warnings and Precautions (5.5)*]

95 **6.1 Clinical Trials Experience**

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

99 The safety of ALECENSA was evaluated in 253 patients with ALK-positive non-small cell lung cancer
100 (NSCLC) treated with ALECENSA 600 mg orally twice daily in two clinical trials, Studies 1 and 2. The median
101 duration of exposure to ALECENSA was 9.3 months. One hundred sixty-nine patients (67%) were exposed to
102 ALECENSA for more than 6 months, and 100 patients (40%) for more than one year. The population
103 characteristics were: median age 53 years, age less than 65 (86%), female (55%), White (74%), Asian (18%),
104 NSCLC adenocarcinoma histology (96%), never or former smoker (98%), ECOG Performance Status (PS) 0 or
105 1 (91%), and prior chemotherapy treatment (78%).

106 Serious adverse reactions occurred in 19% of patients; the most frequently reported serious adverse reactions
107 were pulmonary embolism (1.2%), dyspnea (1.2%), and hyperbilirubinemia (1.2%). Fatal adverse reactions
108 occurred in 2.8% of patients and included hemorrhage (0.8%), intestinal perforation (0.4%), dyspnea (0.4%),
109 pulmonary embolism (0.4%), and endocarditis (0.4%). Permanent discontinuation of ALECENSA for adverse
110 reactions occurred in 6% of patients. The most frequent adverse reactions that led to permanent discontinuation
111 were hyperbilirubinemia (1.6%), increased ALT levels (1.6%), and increased AST levels (1.2%). Overall, 23%
112 of patients initiating treatment at the recommended dose required at least one dose reduction. The median time
113 to first dose reduction was 48 days. The most frequent adverse reactions that led to dose reductions or
114 interruptions were elevations in bilirubin (6%), CPK (4.3%), ALT (4.0%), and AST (2.8%), and vomiting
115 (2.8%).

116 Table 3 summarizes adverse reactions in Studies 1 and 2.

117 **Table 3. Adverse Reactions in $\geq 10\%$ (All Grades) or $\geq 2\%$ (Grade 3-4) of Patients in Studies 1 and 2**

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

118 * Per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

119 ^a Includes fatigue and asthenia.

120 ^b Includes peripheral edema, edema, generalized edema, eyelid edema, and periorbital edema.

121 ^c Includes myalgia and musculoskeletal pain.

122 ^d Includes rash, maculopapular rash, acneiform dermatitis, erythema, generalized rash, papular rash, pruritic rash, and macular rash.

123 ^e Includes one Grade 5 event

124 ^f Includes blurred vision, vitreous floaters, visual impairment, reduced visual acuity, asthenopia, and diplopia.

125

126 **Additional safety information from clinical trial experience**

127 Photosensitivity occurred in 9.9% of patients exposed to ALECENSA in Studies 1 and 2. Patients were advised
128 to avoid sun exposure and to use broad-spectrum sunscreen. The incidence of Grade 2 photosensitivity was
129 0.4%; the remaining events were Grade 1 in severity.

130 Table 4 summarizes laboratory abnormalities of ALECENSA in Studies 1 and 2.

131 **Table 4. Laboratory Abnormalities Occurring in >20% of Patients in Studies 1 and 2**

Parameter	Alectinib 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

132 * Per CTCAE version 4.0

133 ^a n=218 for CPK (with baseline values missing for 91 of these patients).

134 ^b n=152 for fasting blood glucose (with baseline values missing for 5 of these patients).

135 ^c Only patients with creatinine increases based on ULN definition.

136 ^d n=217 for lymphocytes (with baseline values missing for 5 of these patients).

137
138 **7 DRUG INTERACTIONS**

139 No pharmacokinetic interactions with alectinib requiring dosage adjustment have been identified [*see Clinical*
140 *Pharmacology (12.3)*].

141
142 **8 USE IN SPECIFIC POPULATIONS**

143 **8.1 Pregnancy**

144 Risk Summary

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

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

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

154 Data

155 *Animal Data*

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

167 **8.2 Lactation**

168 Risk Summary

169 There are no data on the presence of alectinib or its metabolites in human milk, the effects of alectinib on the
170 breast-fed infant, or its effects on milk production. Because of the potential for serious adverse reactions in
171 breast-fed infants from alectinib, advise a lactating woman not to breastfeed during treatment with ALECENSA
172 and for 1 week after the final dose.

173 **8.3 Females and Males of Reproductive Potential**

174 Contraception

175 *Females*

176 ALECENSA can cause fetal harm when administered to a pregnant woman. Advise females of reproductive
177 potential to use effective contraception during treatment with ALECENSA and for 1 week after the final dose
178 [*see Use in Specific Populations (8.1)*].

179 *Males*

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

183 **8.4 Pediatric Use**

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

185 *Animal Data*

186 Juvenile animal studies have not been conducted using alectinib. In general toxicology studies, treatment of rats
187 with doses of alectinib resulting in exposures greater than or equal to approximately 4.5 times those in humans
188 treated with alectinib at 600 mg twice daily resulted in changes in the growing teeth and bones. Findings in
189 teeth included discoloration and changes in tooth size along with histopathological disarrangement of the
190 ameloblast and odontoblast layers. There were also decreases in the trabecular bone and increased osteoclast
191 activity in the femur and sternum.

192 **8.5 Geriatric Use**

193 Clinical studies of ALECENSA did not include sufficient number of subjects aged 65 and older to determine
194 whether they respond differently from younger subjects.

195

196

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

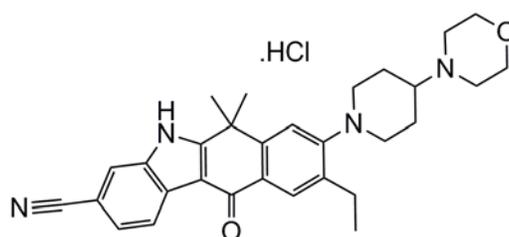
No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin less than or equal to upper limit of normal (ULN) and aspartate transaminase (AST) greater than ULN or total bilirubin greater than 1.0 to 1.5 times ULN and any AST). The safety of ALECENSA in patients with moderate or severe hepatic impairment has not been studied [see *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 $C_{30}H_{34}N_4O_2 \cdot HCl$. 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-5H-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.

240 **12.2 Pharmacodynamics**

241 Cardiac Electrophysiology

242 The ability of alectinib to prolong the QT interval was assessed in 221 patients administered ALECENSA 600
243 mg twice daily in clinical studies. ALECENSA did not prolong the QTc (QT corrected for heart rate) interval to
244 any clinically relevant extent. One patient had a maximum post-baseline QTcF value of greater than 500 msec
245 and one patient had a maximum QTcF change from baseline of greater than 60 msec.

246 **12.3 Pharmacokinetics**

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

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

256 Absorption

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

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

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

262 Distribution

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

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

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

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

270 Elimination

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

273 Metabolism

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

277 Excretion

278 Ninety-eight percent of the radioactivity was excreted in feces following oral administration of a single
279 radiolabeled dose of alectinib under fed conditions. Eighty-four percent of the dose was excreted in the feces as
280 unchanged alectinib and 6% of the dose was excreted as M4. Excretion of radioactivity in urine was less than
281 0.5% of administered radiolabeled dose of alectinib.

282 Specific Populations

283 Age, body weight, mild hepatic impairment, mild to moderate renal impairment (creatinine clearance 30 to 89
284 mL/min), race (White, Asian, and Other), and sex had no clinically meaningful effect on the systemic exposure
285 of alectinib and M4. The pharmacokinetics of alectinib has not been studied in patients with severe renal
286 impairment, end-stage renal disease or moderate to severe hepatic impairment [*see Use in Specific Populations*
287 (8.6, 8.7)].

288 Drug Interactions

289 *Effect of Other Drugs on Alectinib*

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

293 *Effect of Alectinib on Other Drugs*

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

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

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

299 **13 NONCLINICAL TOXICOLOGY**

300 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

301 Carcinogenicity studies with alectinib have not been conducted.

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

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

308 **14 CLINICAL STUDIES**

309 The safety and efficacy of ALECENSA were established in two single-arm, multicenter clinical trials (Studies 1
310 and 2). Patients with locally advanced or metastatic ALK-positive NSCLC, who have progressed on crizotinib,
311 with documented ALK positive NSCLC based on an FDA-approved test, and ECOG PS of 0-2 were enrolled in
312 both studies. Eligibility criteria permitted enrollment of patients with prior chemotherapy and prior CNS
313 radiotherapy provided that CNS metastases were stable for at least two weeks. All patients received
314 ALECENSA 600 mg orally twice daily. The major efficacy outcome measure in both studies was objective
315 response rate (ORR) according to Response Evaluation Criteria in Solid Tumours (RECIST v1.1) as evaluated
316 per Independent Review Committee (IRC). Additional outcome measures as evaluated by the IRC included
317 duration of response (DOR), CNS ORR, and CNS DOR.

318 Study 1 was conducted in North America and enrolled 87 patients. Baseline demographic and disease
319 characteristics in Study 1 were median age 54 years old (range 29 to 79, 18% 65 and over), 84% White and 8%
320 Asian, 55% female, 35% ECOG PS 0 and 55% ECOG PS 1, 100% never or former smokers, 99% Stage IV,
321 94% adenocarcinoma, and 74% prior chemotherapy. The most common sites of extra-thoracic metastasis
322 included 60% CNS (of whom 65% had received CNS radiation), 43% lymph nodes, 36% bone, and 34% liver.

Study 2 was conducted internationally and enrolled 138 patients. Baseline demographic and disease characteristics in Study 2 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 Studies 1 and 2 in all treated patients are summarized in Table 5. The median duration of follow-up on Study 1 was 4.8 months for both IRC and Investigator assessments and on Study 2, 10.9 months for IRC assessment and 7.0 months for Investigator assessment. All responses were partial responses.

Table 5: Efficacy Results in Studies 1 and 2

Efficacy Parameter	Study 1 (N=87)		Study 2 (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 Study 1 and 16 patients in Study 2 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 Studies 1 and 2 with baseline measurable lesions in the CNS according to RECIST v1.1 are summarized in Table 6. 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 6: CNS Objective Response in Patients with Measurable CNS Lesions in Studies 1 and 2

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 evaluable)

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).

349 Inform patients of the following:

350 Hepatotoxicity

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

354 Interstitial Lung Disease (ILD)/Pneumonitis

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

357 Bradycardia

358 Inform patients that symptoms of bradycardia including dizziness, lightheadedness, and syncope can occur
359 while taking ALECENSA. Advise patients to contact their healthcare provider to report these symptoms and to
360 inform their healthcare provider about the use of any heart or blood pressure medications [see *Warnings and*
361 *Precautions (5.3)*].

362 Severe Myalgia/CPK elevation

363 Inform patients of signs and symptoms of myalgia, including unexplained and/or persistent muscle pain,
364 tenderness, or weakness. Advise patients to contact their healthcare provider immediately to report new or
365 worsening symptoms of muscle pain or weakness [see *Warnings and Precautions (5.4)*].

366 Photosensitivity

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

371 Embryo-Fetal Toxicity

372 ALECENSA can cause fetal harm if taken during pregnancy. Advise a pregnant woman of the potential risk to
373 a fetus [see *Warnings and Precautions (5.5) and Use in Specific Populations (8.1, 8.3)*].

374 Advise females of reproductive potential to use effective contraception during treatment with ALECENSA and
375 for at least 1 week after the last dose of ALECENSA. Advise patients to inform their healthcare provider of a
376 known or suspected pregnancy [see *Warnings and Precautions (5.5) and Use in Specific Populations (8.1, 8.3)*].

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

380 Lactation

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

383 Administration

384 Instruct patients to take ALECENSA twice a day. Advise patients to take ALECENSA with food and to
385 swallow ALECENSA capsules whole [see *Dosage and Administration (2.1)*].

386 Missed Dose

387 Advise patients that if a dose of ALECENSA is missed or if the patient vomits after taking a dose of
388 ALECENSA, patients should be advised not to take an extra dose, but to take the next dose at the regular time
389 [see *Dosage and Administration (2.1)*].

390

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395 South San Francisco, CA 94080-4990

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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).** ALECENSA may cause liver injury. Your healthcare provider will do blood tests at least every 2 weeks for the first 2 months and as needed during treatment with ALECENSA. 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.
- **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 faint during treatment with ALECENSA. Tell your healthcare provider if you take any heart or blood pressure medicines.
- **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.

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 people with non-small cell lung cancer (NSCLC) that.

- has a certain type of abnormal anaplastic lymphoma kinase (ALK) gene, **and**
- has spread to other parts of your body, **and**
- who have taken the medicine crizotinib, but their NSCLC worsened or they cannot tolerate taking crizotinib.

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. Tell your healthcare provider right away if you become pregnant during treatment with ALECENSA or think you may be pregnant.
 - **Females** who are able to become pregnant should use effective birth control during treatment with ALECENSA and for 1 week after the final dose of ALECENSA.
 - **Males** who have female partners that are able to become pregnant should use effective birth control during treatment with ALECENSA and for 3 months after the final 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 final 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 final dose of ALECENSA. You may burn more easily and get severe sunburns. Use sunscreen and lip balm with a 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:

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

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 you have. It may harm them. You can ask your healthcare provider or pharmacist for more 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.

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This Patient Information has been approved by the U.S. Food and Drug Administration

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