

Getting started

WITH ALECENSA[®] (alectinib)

ALECENSA is an oral medicine you can take after surgery to help keep your ALK+ non-small cell lung cancer from coming back. ALECENSA is designed to target ALK+ disease.



Not a real patient.

In a clinical study that included 257 people with stage 1B to stage 3A ALK+ NSCLC^a who have had their tumors removed, ALECENSA reduced the risk of cancer coming back by 76% compared to traditional chemotherapy.

Indications

Who is ALECENSA for?

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 doctor 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.

^aALK+ NSCLC=non-small cell lung cancer that is positive for the biomarker called anaplastic lymphoma kinase.

Select Important Safety Information

What are the most serious side effects of ALECENSA?

ALECENSA may cause serious side effects, including:

- Liver problems (hepatotoxicity)
- Lung problems
- Kidney problems
- Slow heartbeat (bradycardia)
- Muscle pain, tenderness, and weakness (myalgia)
- Breakdown of healthy red blood cells earlier than normal (hemolytic anemia)

Please see additional Important Safety Information on pages 14-15, and in full Prescribing Information, including Patient Information, in the pocket.



Getting started **WITH ALECENSA**

A cancer diagnosis can be overwhelming, and it's normal to feel unsure of what the future holds. This guide was created to help you understand your path forward with ALECENSA.

ALECENSA is an after-surgery treatment for certain people with **ALK+ early-stage non-small cell lung cancer** (often called ALK+ eNSCLC). ALK+ NSCLC is a type of NSCLC that is caused by alterations of the *ALK* gene.

The information here will help explain the difference treatment after surgery could make. Talk to your doctor to see if ALECENSA is right for you, and keep this brochure handy as you begin to prepare for the next steps ahead.

**The goal of treatment after surgery is to
HELP KEEP YOU DISEASE-FREE FOR LONGER**

Keep in mind that even if you get adjuvant treatment, the cancer may still return. In addition, some people may experience serious or common side effects while receiving adjuvant treatment.



Not a real patient.

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Throughout this brochure, you'll see **highlighted words**. Definitions for those words can be found in the Glossary on pages 22-23

Select Important Safety Information

ALECENSA may cause serious side effects, including:

Liver problems (hepatotoxicity). Liver problems are common with ALECENSA and can be severe. Your doctor 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 doctor 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

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What is **ALECENSA**?

ALECENSA is not a traditional chemotherapy. It works differently than chemotherapy. ALECENSA is an **ALK inhibitor**. ALK inhibitors work by targeting and blocking the abnormal ALK proteins responsible for the growth and spread of ALK+ NSCLC. This is important to know because the type of cancer you have, ALK+ NSCLC, may be treated by medications that target ALK.

ALECENSA is an oral medicine that is prescribed as an **adjuvant treatment. This means that ALECENSA is used to help prevent your lung cancer from coming back after your tumor has been removed by surgery.**

Select Important Safety Information

ALECENSA may cause serious side effects, including:

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 doctor right away if you have any new or worsening symptoms, including trouble breathing, shortness of breath, cough, or fever.

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Why did my doctor **PRESCRIBE ALECENSA?**

Understanding the goal of treatment after surgery

You have likely either just completed surgery for your ALK+ eNSCLC or are scheduled to get surgery soon. Surgery is very important because it removes the visible tumor(s). But sometimes, there are hidden, microscopic cancer cells that weren't seen or found during surgery. Those microscopic cells can turn into a cancer **recurrence**. This is when cancer comes back after surgery or treatment.



Sometimes cancer comes back, even after a successful surgery. Adjuvant treatment is an additional step you and your doctor can take to help lower the chance of that happening



How can **ALECENSA TREAT MY ALK+ NSCLC?**

One of the goals of adjuvant treatment is **disease-free survival**. This is a measurement of time after starting treatment during which a person is alive with no sign of cancer.

In a clinical study of 257 people with stage 1B to stage 3A ALK+ NSCLC that was **resectable**, or able to be removed with surgery (all of the people included in the study had had their tumors removed by surgery):

**ALECENSA
LOWERED
the chances of
cancer coming back
by 76% compared
to traditional
chemotherapy^a**



Lowering the chances means that people in the study taking ALECENSA were less likely to have their cancer return compared to people taking traditional chemotherapy.

^aPeople in the study received either ALECENSA or a platinum-containing chemotherapy, which is a common adjuvant treatment for NSCLC.

Another analysis measured the number of people who were living without their cancer returning at 2 years:

94% of people on ALECENSA compared to **64% of people on traditional chemotherapy**

There are limitations with these 2-year data. These results are descriptive, which means that researchers looked at what happened in the clinical trial without determining a definitive benefit. Your experiences may differ. Talk to your doctor about how to best understand these results.

ALECENSA
may help
**KEEP YOUR CANCER
FROM COMING BACK
AFTER SURGERY**



Not a real patient.

Select Important Safety Information

ALECENSA may cause serious side effects, including:

Kidney problems. ALECENSA may cause severe kidney problems that can lead to death. Tell your doctor 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.

Please see additional Important Safety Information on pages 14-15, and in full Prescribing Information, including Patient Information, in the pocket.





Not a real patient.

Another goal of adjuvant treatment is keeping cancer from spreading to the **central nervous system (CNS), which is made up of the brain and spinal cord**. This is called CNS recurrence. In NSCLC, it's not uncommon for CNS recurrence to happen.

As observed in the study:

People taking ALECENSA were 78% less likely to experience CNS recurrence than those taking traditional chemotherapy



At the time of recurrence, there were 4 people on ALECENSA (3%) and 14 people on traditional chemotherapy (11%) with disease recurrence in the brain.

These results are descriptive, which means that researchers looked at what happened in the clinical trial without determining a definitive benefit. Your experiences may differ. Talk to your doctor about how to best understand these results.

Select Important Safety Information

ALECENSA may cause serious side effects, including:

Slow heartbeat (bradycardia). ALECENSA may cause very slow heartbeats that can be severe. Your doctor will check your heart rate and blood pressure during treatment with ALECENSA. Tell your doctor right away if you feel dizzy, lightheaded, or if you faint during treatment with ALECENSA. Tell your doctor if you take any heart or blood pressure medicines.

Please see additional Important Safety Information on pages 14-15, and in full Prescribing Information, including Patient Information, in the pocket.



What should I TELL MY DOCTOR?

Before you take ALECENSA, tell your doctor 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 doctor 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 doctor 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 doctor about the best way to feed your baby during this time

Tell your doctor about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements.

Please see Important Safety Information on pages 14-15, and in full Prescribing Information, including Patient Information, in the pocket.



What do I need to know ABOUT TAKING ALECENSA?

It's important to take ALECENSA exactly as your doctor tells you to take it. Do not change your dose or stop taking ALECENSA unless your doctor tells you to. Here are some instructions for taking and storing ALECENSA:



- Take ALECENSA twice a day
- The standard dose of ALECENSA is four 150-mg capsules. The total dose is 600 mg
- You will take 2 doses of ALECENSA each day, for a total of 1200 mg (eight capsules)
- Take ALECENSA exactly as your doctor tells you to take it
- If you have severe liver disease, your doctor may start you on a different dose
- No food interactions have been identified. During clinical trials, participants were not instructed on which foods or how much food to eat when taking ALECENSA
- For questions about how to take ALECENSA, talk to your doctor or care team

i Your doctor may change your dose of ALECENSA or tell you to stop taking ALECENSA depending on how your treatment is going



Please see Important Safety Information on pages 14-15, and in full Prescribing Information, including Patient Information, in the pocket.

Additional important instructions



What to do if you miss a dose:

- If you miss a dose of ALECENSA, **do not take** the missed dose
- Take your next dose at your regular time



What to do if you vomit after a dose:

- If you vomit after taking a dose of ALECENSA, **do not take** an extra dose
- Take your next dose at your regular time



Things to remember:

- Take ALECENSA exactly as your doctor tells you to
- Do not change your dose or stop taking ALECENSA unless your doctor tells you to
- Your doctor may change your dose, temporarily stop, or permanently stop treatment with ALECENSA
- Swallow ALECENSA capsules whole. Do not open or dissolve the capsule contents



How to store ALECENSA

Store ALECENSA:

- In original container
- In a dry place
- Away from light
- Store ALECENSA at or below 86° F (30° C)
- If you think your medicine was exposed to extreme temperatures, contact your pharmacy



Contact the specialty pharmacy if you have questions about storing or shipping ALECENSA.

Make sure you take and return all calls from the specialty pharmacy. Add their phone number to your contacts so that you can recognize and answer their calls promptly. Any delay in communication could mean a delay in you getting your medicine.

If you're not home to receive packages, your specialty pharmacy may be able to deliver your medicine to your local retail pharmacy for you to pick up at your convenience. If they don't suggest that as an option, you can request it.

What are POSSIBLE SIDE EFFECTS?

Learn about the side effects of ALECENSA so you can take note of any that you experience and discuss them with your care team.

Important Safety Information

Tell your doctor right away if you have any new or worsening symptoms such as those described below.

Possible serious side effect:



Liver problems (hepatotoxicity)

Liver problems are common with ALECENSA and can be severe. Your doctor 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 doctor 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.

- Trouble breathing
- Shortness of breath
- Cough
- Fever



Kidney problems

ALECENSA may cause severe kidney problems that can lead to death.

- A change in the amount or color of your urine
- New or worsening swelling in your legs or feet

Possible serious side effect:



Slow heartbeat (bradycardia)

ALECENSA may cause very slow heartbeats that can be severe. Your doctor will check your heart rate and blood pressure during treatment with ALECENSA. Tell your doctor if you take any heart or blood pressure medications.

Tell your doctor right away if you get any of the following signs and symptoms:

- Feeling dizzy
- Feeling lightheaded
- If you faint during treatment with ALECENSA



Severe muscle pain, tenderness, and weakness (myalgia)

Muscle problems are common with ALECENSA and can be severe. Your doctor will do blood tests at least every 2 weeks for the first month and as needed during treatment with ALECENSA.

- Unexplained muscle pain
- Muscle pain that does not go away
- Tenderness
- 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 doctor may temporarily stop ALECENSA and do blood tests, if needed, to check for this problem. If you develop hemolytic anemia, your doctor may either restart you on ALECENSA at a lower dose when the hemolytic anemia goes away, or may stop your treatment with ALECENSA.

- Yellow skin (jaundice)
- Weakness
- Dizziness
- Shortness of breath

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 doctor or pharmacist. Call your doctor for medical advice about side effects.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

What can I do about COMMON SIDE EFFECTS?

Your care team is the best resource for any questions you may have. In addition, we've provided guidance for some side effects that may occur while taking ALECENSA.

This is not medical advice or a replacement for your care team's advice. Open communication with your care team is key for a successful treatment experience.

What should I do if I'm concerned about liver problems?

Your doctor may have told you that liver problems are common with treatment or you may have had your liver tests come back already. Changing lifestyle habits may help improve liver health. Here are some suggestions:



- Limit alcohol consumption
- Eat fruits, vegetables, and whole grains
- Limit foods with sugar or fructose
- Eat healthier fats, such as olive oil and walnuts. Limit red meat
- Maintain a healthy weight

Should I avoid being in the sunlight while taking ALECENSA?



- You may burn more easily and get severe sunburns, so avoid spending time in the sunlight during treatment with ALECENSA and for 7 days after the final dose of ALECENSA
- Use sunscreen and lip balm with SPF 50 or greater to help protect against sunburn
- Wear a long-sleeved shirt, long pants and/or skirts, and a wide-brimmed hat to help protect your skin from UV rays

How can I combat my tiredness or fatigue?



- Talk to your doctor about how to stay active
- Practice mind-body strategies, like meditation
- Work with a physical therapist
- Talk with a counselor

How should I deal with constipation?



- Drink more liquids; water is best
- Eat more fiber like whole grains, vegetables, fruit, and nuts
- Increase your physical activity
- Talk to your doctor about fiber supplements or laxatives

What if I get swelling in my hands, feet, ankles, face, or eyelids (edema)?



- Limit salt in your diet
- Ask your doctor for specific exercises to help with circulation
- Raise your feet when resting
- Wear loose clothing around swollen areas
- Wear compression socks, sleeves, or gloves that help with circulation and may help with severe swelling

What can I do if I have muscle pain, tenderness, or weakness (myalgia)?



- Get a massage or physical therapy
- Do light exercise
- Apply heat or cold
- Try relaxation techniques; sometimes even a few deep breaths can help
- Talk to your doctor about medications to treat muscle aches and reduce the pain

Is there something I can do if I have a low red blood cell count (anemia)?



- Eat foods that are good sources of iron
- Talk to your doctor about treatment options like medication or supplements



It's important to talk to your doctor before taking any action to minimize side effects

Please see Important Safety Information on pages 14-15, and in full Prescribing Information, including Patient Information, in the pocket.



How can Genentech SUPPORT ME?

ACCESS SOLUTIONS®

Genentech Access Solutions is a program that helps people who are taking a Genentech medicine like ALECENSA. It can help by:

Checking your coverage and costs

We can find out if your health insurance plan covers your medicine and how much your out-of-pocket costs will be.

The Genentech Co-pay Assistance Program:

- Helps people with commercial health insurance (also known as private health insurance)
- Has zero income requirements
- To find out if you qualify, call (855) MYCOPAY (692-6729), or visit copayassistancenow.com



Helping you find ways to pay

We can refer you to financial assistance programs to help you pay for your medicine.

The Independent Co-pay Assistance Foundation:

- Helps people with public health insurance or commercial health insurance by referring them to an independent co-pay assistance foundation
- You can visit Genentech-Access.com to view a list of independent co-pay assistance foundations or call (888) 249-4918 to get help

The Genentech Patient Foundation:

- Is a program that gives free Genentech medicine to people who don't have insurance coverage or have financial concerns and meet certain eligibility criteria
- To learn more and to apply for help, visit genentechpatientfoundation.com



Working to get your medicine to you

We work with your doctor's office and/or your specialty pharmacy to help you get your medicine.

If a specialty pharmacy is used for ALECENSA, they may call you to find out:

- How to have your ALECENSA sent to your home
- How you will pay for your medicine and what type of insurance you have
- If you need help paying for your medicine
- If you have any questions about your medicine

**NO INCOME
REQUIREMENTS**



Pay as little as
\$0
PER CO-PAY

\$25K
ANNUAL BENEFIT LIMIT
per Genentech product



Please see Important Safety Information on pages 14-15, and in full Prescribing Information, including Patient Information, in the pocket.

The Co-pay Program ("Program") is valid ONLY for patients with commercial (private or non-governmental) insurance who have a valid prescription for a Food and Drug Administration (FDA)-approved indication of a Genentech medicine. Patients using Medicare, Medicaid or any other federal or state government program (collectively, "Government Programs") to pay for their Genentech medicine are not eligible.

Under the Program, the patient may be required to pay a co-pay. The final amount owed by a patient may be as little as \$0 for the Genentech medicine (see Program specific details available at the Program website). The total patient out-of-pocket cost is dependent on the patient's health insurance plan. The Program assists with the cost of the Genentech medicine only. It does not assist with the cost of other medicines, procedures or office visit fees. After reaching the maximum annual Program benefit amount, the patient will be responsible for all remaining out-of-pocket expenses. The Program benefit amount cannot exceed the patient's out-of-pocket expenses for the Genentech medicine.

All participants are responsible for reporting the receipt of all Program benefits as required by any insurer or by law. The Program is only valid in the United States and U.S. Territories, is void where prohibited by law and shall follow state restrictions in relation to AB-rated generic equivalents (e.g., MA, CA) where applicable. No party may seek reimbursement for all or any part of the benefit received through the Program. The value of the Program is intended exclusively for the benefit of the patient. The funds made available through the Program may only be used to reduce the out-of-pocket costs for the patient enrolled in the Program. The Program is not intended for the benefit of third parties, including without limitation third party payers, pharmacy benefit managers, or their agents. If Genentech determines that a third party has implemented a program that adjusts patient cost-sharing obligations based on the availability of support under the Program and/or excludes the assistance provided under the Program from counting towards the patient's deductible or out-of-pocket cost limitations, Genentech may impose a per fill cap on the cost-sharing assistance available under the Program. Submission of true and accurate information is a requirement for eligibility and Genentech reserves the right to disqualify patients who do not comply from Genentech programs. Genentech reserves the right to rescind, revoke or amend the Program without notice at any time.

Additional terms and conditions apply. Please visit the Co-pay Program website for the full list of Terms and Conditions.

Where can I go FOR MORE SUPPORT?

Genentech's **Staying Positive** support program provides helpful information about ALECENSA, additional resources, and practical tips on living with resectable ALK+ NSCLC:

- Through emails, you can receive **advice from real people living with resectable ALK+ NSCLC** on sharing their diagnosis with loved ones, how they cope with scan anxiety, practicing self-care, and more



Find out more at alecensa.com/stayingpositive



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Who else can provide support?

Many organizations offer helpful information about lung cancer and support for patients and their loved ones. A few of these include:



ALK Positive
alkpositive.org

ALK Positive is a community of patients and caregivers, family, and friends affected by ALK+ lung cancer. They share experiences, knowledge, and emotional support with the hope of improving quality of life.



The LUNGevity Foundation
lungevity.org | (844) 360-5864

The LUNGevity Foundation works to make an immediate impact on increasing quality of life and survivorship of people with lung cancer by providing community, support, and education for all affected by the disease.



GO₂ Foundation for Lung Cancer
go2foundation.org | (800) 298-2436

The GO₂ Foundation for Lung Cancer works to change life with lung cancer by ending stigma, increasing public and private research funding, and ensuring access to care.

Genentech does not control or endorse the content of the third-party websites listed above, and Genentech makes no representation as to the accuracy of the information contained on these websites. The information provided by these organizations is meant for informational purposes only and is not meant to replace a doctor's medical advice. Your use of third-party websites is at your own risk and subject to the terms and conditions of use for such sites.

Caregiver support IS DEEPLY IMPORTANT

Your caregiver may be a spouse, partner, child, or another loved one. They may not know what you need or how to help. It's important to keep the lines of communication open and honest, so you can share with them how they can help you best.

Not a real patient.



Glossary

OF IMPORTANT TERMS

Adjuvant treatment: Treatment given after surgery to help lower the risk that the cancer will come back.

ALK (anaplastic lymphoma kinase): The *ALK* gene makes an ALK protein, which may be involved in signaling cell growth. Mutations of the *ALK* gene have been associated with certain types of cancer, including non-small cell lung cancer, sometimes referred to as NSCLC.

ALK inhibitor: An ALK inhibitor is a type of medicine that is designed to bind to and block the activity of the ALK protein.

ALK+ NSCLC: ALK (anaplastic lymphoma kinase positive) non-small cell lung cancer is a type of lung cancer involving a mutation in the *ALK* gene.

Central nervous system (CNS): The central nervous system includes the brain and the spinal cord.

Co-pay: An amount you have to pay for healthcare services or medicines. You pay this amount after you pay your deductible. A co-pay is usually a set dollar amount.

Disease-free survival (DFS): The amount of time after starting treatment when a person is alive and no cancer is found.

eNSCLC (early-stage non-small cell lung cancer): This when cancer is in stages 1, 2, or 3A. In the early stages, the tumor remains in the lung and may not have spread to lymph nodes outside of the lung.

NSCLC (non-small cell lung cancer): A cancer that grows from inside your lungs, usually in the cells lining air passages. Not all lung cancers are classified as non-small cell. This is determined by a biopsy of tumor tissue.

Recurrence: When cancer comes back after surgery or treatment.

Resectable: A tumor that is able to be removed with surgery.



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Who can I contact WITH QUESTIONS?

Your doctor is the best resource for any questions you may have about treatment with ALECENSA.



Speak with one of our live representatives

who can guide you to the resources you need

ALECENSA Patient Resource Center:
(800) ALECENSA (253-2367);
translation services are available

Monday-Friday, 9 AM-8 PM ET



Ask nurse-specific medical questions related to your Genentech medicine

Genentech: (800) 821-8590

Monday-Friday, 8 AM-8 PM ET

Genentech is unable to provide treatment advice. If you have questions about your medical condition, contact your doctor.



Report side effects

FDA: (800) FDA-1088 or
www.fda.gov/medwatch

Genentech: (888) 835-2555

7 days/week, 24 hours/day

You are not alone. Along with your healthcare team and caregivers, we are here to support you on your path forward with ALECENSA.



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“It’s very important to have a positive mind.

It’s not always easy to do, but I think that positivity does have an impact on how you get through the difficult days.”

—Colleen

A real patient who took ALECENSA for metastatic NSCLC.



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**For more information, scan the QR code
or visit www.ALECENSA.com**

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**ALECENSA**[®]
alectinib 150 mg
capsules

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

-----RECENT MAJOR CHANGES-----

Indications and Usage (1.1)	04/2024
Dosage and Administration (2.1, 2.2, 2.3)	04/2024
Warnings and Precautions (5)	04/2024

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

ALECENSA is a kinase inhibitor indicated for:

- adjuvant treatment in adult patients following tumor resection of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) (tumors \geq 4 cm or node positive) as detected by an FDA-approved test. (1.1)
- treatment of adult patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test. (1.2)

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

600 mg orally twice daily. Administer ALECENSA with food. (2.2)

-----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 3 months of treatment, then once a month and as clinically indicated, with more frequent testing in patients who develop transaminase and bilirubin elevations. In case of severe ALT, AST, or bilirubin elevations,

withhold, then reduce dose, or permanently discontinue ALECENSA. (2.4, 5.1)

- Interstitial Lung Disease (ILD)/Pneumonitis: Immediately withhold ALECENSA in patients diagnosed with ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis have been identified. (2.4, 5.2)
- Renal Impairment: Withhold ALECENSA for severe renal impairment, then resume ALECENSA at reduced dose upon recovery or permanently discontinue (2.4, 5.3).
- Bradycardia: Monitor heart rate and blood pressure regularly. If symptomatic, withhold ALECENSA then reduce dose, or permanently discontinue. (2.4, 5.4)
- Severe Myalgia and Creatine Phosphokinase (CPK) Elevation: 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. (2.4, 5.5)
- Hemolytic Anemia: If hemolytic anemia is suspected, withhold ALECENSA. If hemolytic anemia is confirmed, consider resuming at a reduced dose upon resolution or permanently discontinue. (5.6)
- 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. (5.7, 8.1, 8.3)

-----ADVERSE REACTIONS-----

The most common adverse reactions (incidence \geq 20%) were hepatotoxicity, constipation, fatigue, myalgia, edema, rash and cough. (6.1)

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 SPECIFIC POPULATIONS-----

Lactation: Do not breastfeed. (8.2)

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

Revised: 04/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Adjuvant Treatment of Resected ALK-Positive NSCLC
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2 DOSAGE AND ADMINISTRATION

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Adjuvant Treatment of Resected ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

ALECENSA is indicated as adjuvant treatment in adult patients following tumor resection of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) (tumors \geq 4 cm or node positive), as detected by an FDA-approved test [see *Dosage & Administration (2.1)*].

1.2 Treatment of Metastatic ALK-Positive NSCLC

ALECENSA is indicated for the treatment of adult patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test [see *Dosage & Administration (2.1)*].

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients with resectable tumors for the adjuvant treatment of NSCLC with ALECENSA based on the presence of ALK positivity in tumor tissue [see *Indications and Usage (1.1)* and *Clinical Studies (14.1)*].

Select patients for the treatment of metastatic NSCLC with ALECENSA based on the presence of ALK positivity in tumor tissue or plasma specimens [see *Indications and Usage (1.2)* and *Clinical Studies (14.2)*]. If ALK rearrangements are not detected in a plasma specimen, test tumor tissue if feasible.

Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at <http://www.fda.gov/CompanionDiagnostics>.

2.2 Dosing and Administration

The recommended dosage information for ALECENSA is provided in Table 1.

Table 1: ALECENSA Recommended Dosage and Duration of Treatment

Indication	Recommended Dosage of ALECENSA	Duration
Adjuvant treatment of resected NSCLC	600 mg orally twice daily with food [see <i>Clinical Pharmacology (12.3)</i>]	For a total of 2 years or until disease recurrence or unacceptable toxicity
Metastatic NSCLC		Until disease progression or unacceptable toxicity
<ul style="list-style-type: none">Swallow capsules whole, do not open or dissolve the contents of the capsule.If a dose of ALECENSA is missed or vomiting occurs after taking a dose of ALECENSA, take the next dose at the scheduled time.		

2.3 Recommended Dosage for Hepatic Impairment

The recommended dose of ALECENSA in patients with severe hepatic impairment (Child-Pugh C) is 450 mg orally twice daily [see *Use in Specific Populations (8.7)* and *Clinical Pharmacology (12.3)*].

2.4 Dose Modifications for Adverse Reactions

The dose reduction schedule for ALECENSA is provided in Table 2.

Table 2: 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

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

Recommendations for dose modifications of ALECENSA in case of adverse reactions are provided in Table 3.

Table 3: 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 2.
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 2.
Any grade treatment-related interstitial lung disease (ILD)/pneumonitis	Permanently discontinue ALECENSA.
Grade 3 renal impairment	Temporarily withhold until serum creatinine recovers to less than or equal to 1.5 times ULN, then resume at reduced dose.
Grade 4 renal impairment	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 2) 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 2) 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 2.
Hemolytic Anemia	Withhold ALECENSA if hemolytic anemia is suspected. Upon resolution, resume at reduced dose or permanently discontinue.

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Severe hepatotoxicity, including drug-induced liver injury, occurred in patients treated with ALECENSA.

In the pooled safety population [see *Adverse Reactions (6.1)*] of patients who received ALECENSA, hepatotoxicity occurred in 41% of patients and the incidence of Grade ≥ 3 hepatotoxicity was 8%. In the ALINA study, hepatotoxicity occurred in 61% of patients treated with ALECENSA and the incidence of Grade ≥ 3 hepatotoxicity was 4.7%. The majority (72% of 136 patients) of elevated transaminases occurred during the first 3 months of treatment. Treatment discontinuation due to hepatotoxicity occurred in 3.6% of patients who received ALECENSA in the pooled safety population and 1.6% of patients treated in the ALINA study.

In the pooled safety population, concurrent elevations in ALT or AST greater than or equal to 3 times the ULN and total bilirubin greater than or equal to 2 times the ULN, with normal alkaline phosphatase, occurred in less than 1% of patients treated with ALECENSA. Three patients with Grades 3–4 AST/ALT elevations had drug-induced liver injury (documented by liver biopsy in two cases).

Monitor liver function tests including ALT, AST, and total bilirubin every 2 weeks during the first 3 months of treatment, then once a month and as clinically indicated, with more frequent testing in patients who develop transaminase and bilirubin elevations. Based on the severity of the adverse drug reaction, withhold ALECENSA and resume at a reduced dose or permanently discontinue ALECENSA as described in Table 3 [see *Dosage and Administration (2.4)*].

5.2 Interstitial Lung Disease (ILD)/Pneumonitis

ILD/pneumonitis occurred in patients treated with ALECENSA.

In the pooled safety population [see *Adverse Reactions (6.1)*], ILD/pneumonitis occurred in 1.3% of patients treated with ALECENSA with 0.4% of patients experiencing Grade 3 ILD/pneumonitis.

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 ($\geq 20\%$) adverse reactions were hepatotoxicity (41%), constipation (39%), fatigue (36%), myalgia (31%), edema (29%), rash (23%) and cough (21%). The most common ($\geq 2\%$) 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 ($\geq 1\%$) 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 ($\geq 1\%$) 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 $\geq 2\%$ 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 $\geq 2\%$ 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 ($\geq 10\%$) 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 $\geq 20\%$ 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 $\geq 10\%$ (All Grades) or $\geq 2\%$ (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_{0-24h,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_{0-24h,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_{0-24h,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

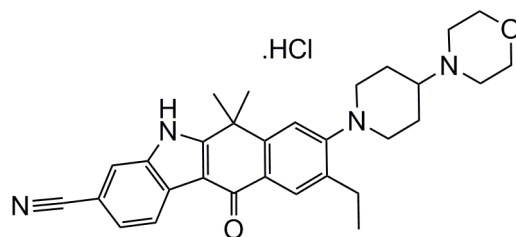
No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Increased exposure of alectinib occurred in patients with severe hepatic impairment (Child-Pugh C). The recommended dose of ALECENSA in patients with severe hepatic impairment (Child-Pugh 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 $C_{30}H_{34}N_4O_2 \cdot HCl$. 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.

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 \leq ULN and AST $>$ ULN or total bilirubin 1 to $\leq 1.5 \times$ 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/m² on Day 1 plus vinorelbine 25 mg/m² on Days 1 and 8
- Cisplatin 75 mg/m² on Day 1 plus gemcitabine 1250 mg/m² on Days 1 and 8
- Cisplatin 75 mg/m² on Day 1 plus pemetrexed 500 mg/m² 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-III A NSCLC and DFS in patients with stage IB-III A 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 III A 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	

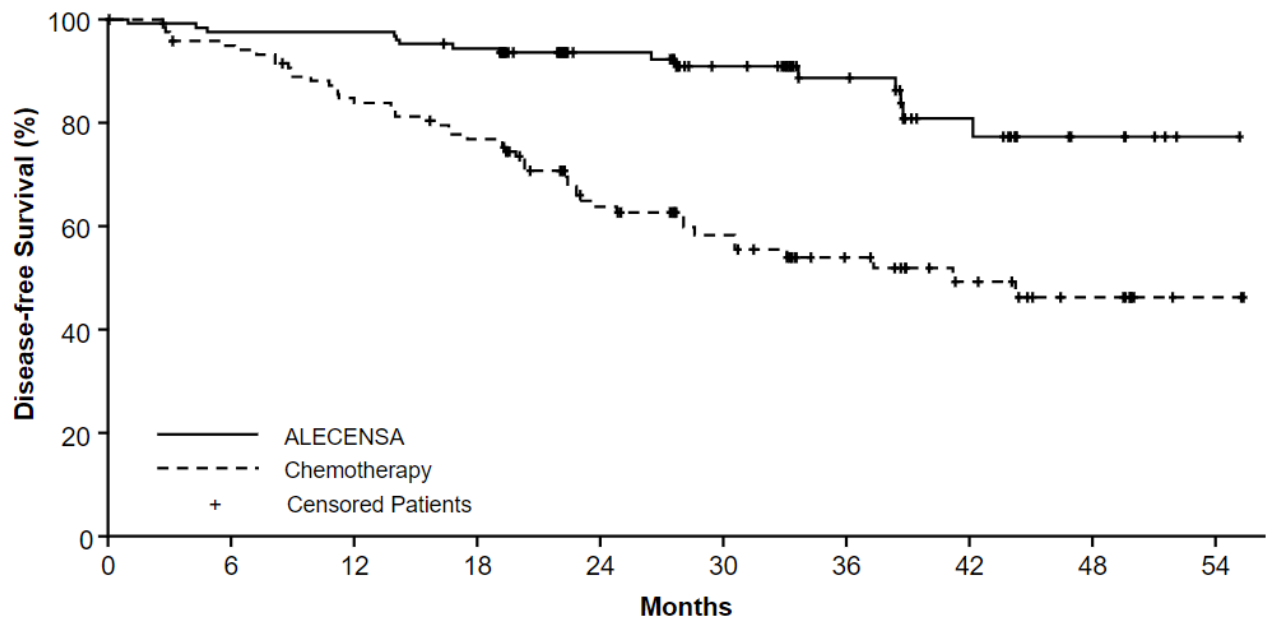
DFS = Disease-Free Survival; ITT = Intent-to-Treat; CI = Confidence Interval; NR = Not Reached; NE = Not Estimable.

^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

	0	6	12	18	24	30	36	42	48	54
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

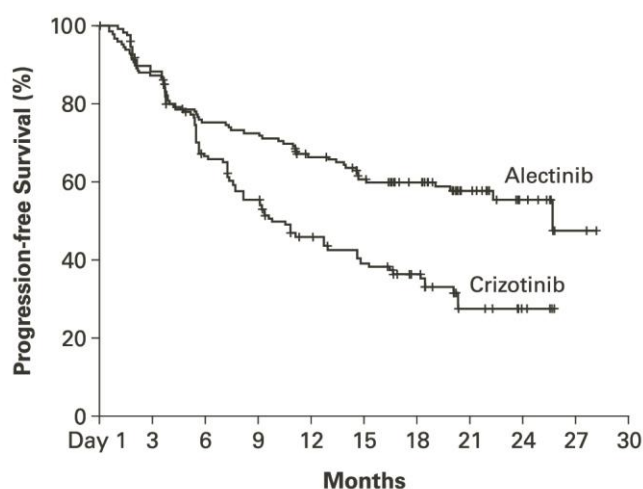
	ALECENSA N=152	Crizotinib N=151
Progression-Free Survival		
Number of events (%)	63 (41%)	92 (61%)
Progressive disease (%)	51 (34%)	82 (54%)
Death (%)	12 (8%)	10 (7%)
Median in months (95% CI)	25.7 (19.9, NE)	10.4 (7.7, 14.6)
Hazard ratio (95% CI) ^a	0.53 (0.38, 0.73)	
P-value ^b	< 0.0001	
Overall Response 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



No. at Risk	
Crizotinib	151 128 92 74 57 46 33 12 4
Alectinib	152 132 112 108 95 83 69 35 15 2

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 \geq 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)*].

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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).** 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.

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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.

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