HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NELKARMI safely and effectively. See full prescribing information for NELKARMI.

NELKARMI™ (neladalkib) tablets, for oral use
Initial U.S. Approval: 2026

----------INDICATIONS AND USAGE----------
NELKARMI is a kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who have previously received the following therapy in the unresectable locally advanced or metastatic setting:

- 1 prior ALK TKI consisting of alectinib; or
- 2 or more prior ALK TKIs and platinum-based chemotherapy

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. (1)

----------DOSAGE AND ADMINISTRATION----------
Recommended Dosage: 150 mg orally once daily with or without food until disease progression or unacceptable toxicity. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 50 mg and 150 mg (3)

----------CONTRAINDICATIONS----------
None. (4)

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

- Hepatotoxicity: Monitor liver laboratory tests (ALT, AST, and total bilirubin) at baseline, every 2 weeks during the first 2 months of treatment, and then monthly thereafter as clinically indicated during treatment with NELKARMI. Withhold, then resume at the same dose or reduced dose, or permanently discontinue NELKARMI based on severity. (5.1)
- Renal Toxicity: Monitor serum creatinine at baseline and every 2 weeks for the first month and then periodically as clinically indicated during treatment with NELKARMI. Withhold, then resume at the same or reduced dose, or permanently discontinue NELKARMI based on severity. (5.2)
- Ocular Toxicity: Monitor for vision changes at regular intervals during treatment with NELKARMI. Promptly refer patients with new or worsening visual symptoms to an eye care professional, such as an ophthalmologist or optometrist. Withhold, then reduce the dose, or permanently discontinue NELKARMI based on severity. (5.3)
- Creatine Phosphokinase Elevation: Monitor serum CPK levels at baseline and every 2 weeks for the first two months, then periodically as clinically indicated during treatment with NELKARMI. Withhold, then resume at the same or reduced dose, or permanently discontinue NELKARMI based on severity. (5.4)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective nonhormonal contraception. (5.5)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥20%) were hepatotoxicity, musculoskeletal pain, constipation, dysgeusia, peripheral neuropathy, edema and fatigue. (6.1)
Most common Grade 3 or 4 laboratory abnormalities (≥2%) were increased alanine aminotransferase, increased aspartate aminotransferase, increased creatine phosphokinase, decreased lymphocytes, decreased potassium, and decreased hemoglobin. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Nuvalent, Inc. at 1-844-NUVL-111 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong and moderate CYP3A Inhibitors: Avoid concomitant use. (7.1)
- Strong and moderate CYP3A Inducers: Avoid concomitant use. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)

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

Revised: 11/2026

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NELKARMI™ (neladalkib) is indicated for the treatment of adult patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who have previously received the following therapy in the unresectable locally advanced or metastatic setting:

- 1 prior ALK TKI consisting of alectinib; or
- 2 or more prior ALK TKIs and platinum-based chemotherapy

This indication is approved under accelerated approval based on tumor response rate and duration of response *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Testing and Evaluation Before Initiating NELKARMI

Before initiating NELKARMI, evaluate liver function tests (ALT, AST, and total bilirubin), serum creatinine, and creatine phosphokinase (CPK) *[see Warnings and Precautions (5.1, 5.2, 5.4)]*.

2.2 Recommended Dosage

The recommended dosage of NELKARMI is 150 mg orally once daily with or without food taken at the same time every day *[see Clinical Pharmacology (12.3)]* until disease progression or unacceptable toxicity.

Swallow tablets whole. Do not split, chew, crush, or dissolve tablets.

Missed Dose

If a dose is missed by more than 12 hours, skip the missed dose and take the next dose at the next scheduled time.

Vomiting

If vomiting occurs after taking a dose, do not take an additional dose. Take the next dose at the next scheduled time.

2.3 Dosage Modifications for Adverse Reactions

The recommended dosage reductions of NELKARMI for the management of adverse reactions are provided in Table 1.

Table 1: Recommended Dose Reductions for NELKARMI Adverse Reactions

First	100 mg once daily
Second*	50 mg once daily

*Permanently discontinue NELKARMI if unable to tolerate 50 mg orally once daily.

Recommended dosage modifications for NELKARMI for the management of adverse reactions are provided in Table 2.

Table 2: Recommended Dosage Modifications of NELKARMI for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
Hepatotoxicity *[see Warnings and Precautions (5.1)]*	Grade 2 or 3 elevations (greater than 3 × ULN) of either ALT or AST with bilirubin less than or equal to 2 × ULN	• Temporarily withhold NELKARMI until recovery to baseline or Grade 1.

Adverse Reaction	Severity*	Dosage Modification
		• Resume NELKARMI at the same dose. • For recurrence at Grade ≥ 2, resume NELKARMI at the next lower dose.
	Grade 4 elevations (greater than 20 x ULN) of either ALT or AST with bilirubin less than or equal to 2 x ULN	• Temporarily withhold NELKARMI until recovery to baseline or Grade 1. • Resume NELKARMI at the next lower dose. • For recurrence of Grade 2, resume at the next lower dose. • For recurrence of Grade ≥ 3, permanently discontinue NELKARMI.
	ALT or AST greater than 3 x ULN with concurrent total bilirubin elevation greater than 2 × ULN in the absence of cholestasis or hemolysis	• Permanently discontinue NELKARMI.
Renal Toxicity *[see Warnings and Precautions (5.2)]*	Grade 3	• Withhold NELKARMI until recovery to baseline or Grade 1. • Resume NELKARMI at the same or next lower dose. • For recurrence, permanently discontinue NELKARMI.
	Grade 4	• Permanently discontinue NELKARMI.
Ocular Toxicity *[see Warnings and Precautions (5.3)]*	Grade 2 Keratitis	• Withhold NELKARMI until recovery to baseline or Grade 1. • Resume NELKARMI at same dose.
	Grade 3 Keratitis	• Withhold NELKARMI until recovery to baseline or Grade 1. • Resume NELKARMI at reduced dose.
	Retinal pigment epithelium detachment (RPED)	• For RPED, continue NELKARMI as current dose. • If RPED persists for > 14 days, reduce NELKARMI dose. • If RPED persists for > 28 days, further reduce NELKARMI dose or withhold until recovery to baseline or Grade 1.
Creatine Phosphokinase Elevation *[see Warnings and Precautions (5.4)]*	Grade 3 or 4	• Withhold NELKARMI until recovery to baseline or Grade ≤ 1. • Grade 3: resume NELKARMI at the same dose. • Grade 4: resume NELKARMI at the next lower dose.

Adverse Reaction	Severity*	Dosage Modification
Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Grade 3 or 4	• Withhold NELKARMI until recovery to baseline or Grade ≤ 1. • Grade 3: resume NELKARMI at the same dose. • Recurrent Grade 3: resume NELKARMI at the next lower dose. • Grade 4: resume NELKARMI at the next lower dose. • Recurrence at Grade ≥ 3: permanently discontinue NELKARMI.

*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 50 mg: orange, oblong, film-coated, debossed with "50" on one side and "NLD" on the other side.
- 150 mg: red, oblong, film-coated, debossed with "150" on one side and "NLD" on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

NELKARMI can cause severe and life-threatening hepatotoxicity, including drug induced liver injury (DILI) resulting in hepatic failure.

In the pooled safety population *[see Adverse Reactions (6.1)]*, based on adverse reaction data, hepatotoxicity occurred in 56% of patients who received NELKARMI, including Grade 3 in 18% and Grade 4 in 7%. Grade 3 or 4 DILI occurred in 0.3%, and Grade 3 or 4 hepatic failure occurred in 0.4%.

Based on laboratory data, increased alanine aminotransferase (ALT) occurred in 62% of patients treated with NELKARMI, including Grade 3 in 13% and Grade 4 in 4.8%. Increased aspartate aminotransferase (AST) occurred in 63% including Grade 3 in 11% and Grade 4 in 2.5% of patients treated with NELKARMI. The median time to first onset of increased ALT or AST was 16 days (range: 6 to 421 days).

NELKARMI was interrupted due to hepatotoxicity in 25% of patients, the dose was reduced in 11% and permanently discontinued in 3%.

Monitor liver function tests (ALT, AST and total bilirubin) at baseline, every 2 weeks during the first 2 months of treatment, and then monthly and as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Withhold, then resume at the same dose or reduced dose, or permanently discontinue NELKARMI based on severity *[see Dosage and Administration (2.1, 2.2)]*.

5.2 Renal Toxicity

NELKARMI can cause severe and life-threatening renal toxicity, including acute kidney injury.

In the pooled safety population *[see Adverse Reactions (6.1)]*, based on adverse reaction data, acute kidney injury occurred in 1.1% of patients who received NELKARMI, including Grade 3 in 0.3%, and Grade 4 in 0.3%. Grade 2 chronic kidney disease occurred in 0.3% of patients.

In the pooled safety population *[see Adverse Reactions (6.1)],* based on laboratory data, increased serum creatinine occurred in 24% of patients who received NELKARMI, including Grade 3 in 0.1% and Grade 4 in 0.3% of patients. The median time to first onset of increased creatinine was 29 days (range: 6 to 364 days).

NELKARMI was interrupted for renal toxicity in 0.6% and permanently discontinued in 0.4% of patients.

Monitor serum creatinine at baseline and every 2 weeks for the first month and then periodically as clinically indicated during treatment with NELKARMI. Withhold, then resume at the same or reduced dose, or permanently discontinue NELKARMI based on severity *[see Dosage and Administration (2.1, 2.2)].*

5.3 Ocular Toxicity

NELKARMI can cause ocular toxicity including retinal detachment, corneal erosion and keratopathy.

In the pooled safety population *[see Adverse Reactions (6.1)],* ocular toxicity occurred in 14% of patients treated with NELKARMI. Grade 2 ocular toxicity occurred in 2.9%, Grade 3 (diplopia, retinal detachment, corneal erosion and keratopathy) was observed in one patient each and Grade 4 (retinal detachment) was observed in one patient. The median time to onset of ocular toxicity was 43 days (range: 1 to 535 days).

NELKARMI was interrupted in 0.7% due to ocular toxicity.

Monitor for vision changes at regular intervals during treatment with NELKARMI. Promptly refer patients with new or worsening visual symptoms to an eye care professional, such as an ophthalmologist or optometrist. Withhold, then reduce the dose, or permanently discontinue NELKARMI based on severity *[see Dosage and Administration (2.2)].*

5.4 Creatine Phosphokinase Elevation

NELKARMI can cause severe creatine phosphokinase (CPK) elevation.

In the pooled safety population *[see Adverse Reactions (6.1)]*, based on laboratory values, increased CPK occurred in 28% of patients who received NELKARMI, including Grade 3 in 2.7% and Grade 4 in 1.2% of patients. The median time to onset of CPK elevation was 43 days (range: 5 days to 478 days).

NELKARMI was interrupted for CPK elevation in 1.9% and the dose was reduced in 0.4% of patients.

Monitor serum CPK levels at baseline and every 2 weeks for the first two months, then periodically as clinically indicated during treatment with NELKARMI. Withhold, then resume at the same or reduced dose, or permanently discontinue NELKARMI based on severity *[see Dosage and Administration (2.1, 2.2)].*

5.5 Embryo-Fetal Toxicity

Based on literature reports in humans with congenital mutations leading to changes in tropomyosin receptor kinase (TRK) signaling, findings from animal studies, and its mechanism of action *[see Clinical Pharmacology (12.1)],* NELKARMI can cause fetal harm when administered to a pregnant woman.

In an animal reproduction study, oral administration of neladalkib to pregnant rats during the period of organogenesis resulted in embryo-fetal mortality, alterations to growth, and structural abnormalities at maternal exposures ≥ 0.7 times the human exposure at the recommended dose based on area under the curve (AUC).

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective nonhormonal contraception during treatment with NELKARMI and for 2 weeks after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with NELKARMI and for 2 weeks after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Renal Toxicity *[see Warnings and Precautions (5.2)]*

- Ocular Toxicity *[see Warnings and Precautions (5.3)]*
- Creatine Phosphokinase Elevation *[see Warnings and Precautions (5.4)]*

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 WARNINGS AND PRECAUTIONS reflects exposure to NELKARMI in 700 patients enrolled in ALKOVE-1 (n=656 with ALK-positive NSCLC *[see Clinical Studies (14.1)]* and n=44 with other ALK-positive solid tumors). Patients received NELKARMI at a dose of 150 mg orally once daily until disease progression or unacceptable toxicity. Among 700 patients who received NELKARMI, 50% were exposed for 6 months or longer and 14% were exposed for greater than one year. In this pooled population, the most common (≥20%) adverse reactions included: hepatotoxicity (56%), musculoskeletal pain (33%), constipation (28%), dysgeusia (24%), peripheral neuropathy (23%), edema (21%), and fatigue (21%). The most common Grade 3 or 4 laboratory abnormalities (≥2%), were increased alanine aminotransferase (18%), increased aspartate aminotransferase (13%), increased creatine phosphokinase (3.9%), decreased lymphocytes (2.5%), decreased potassium (2.3%), and decreased hemoglobin (2.3%).

Locally Advanced or Metastatic ALK-positive Non-Small Cell Lung Cancer

The safety of NELKARMI was evaluated in 656 patients with ALK-positive NSCLC in ALKOVE-1 *[see Clinical Studies (14.1)]*. Patients with ALK-positive NSCLC received NELKARMI 150 mg orally once daily until disease progression or unacceptable toxicity. Among the 656 patients who received NELKARMI, 51% were exposed to NELKARMI for 6 months or longer and 14% were exposed for greater than one year.

The median age of patients who received NELKARMI was 56 years (range: 20 to 83); 56% female; 48% White, 29% Asian, 21% other races or unknown, 2% Black or African American; and 5% were of Hispanic or Latino ethnicity.

Serious adverse reactions occurred in 30% of patients who received NELKARMI. Serious adverse reactions in ≥2% of patients included hepatotoxicity (7%), pneumonia (3.7%), pleural effusion (2.4%), and dyspnea (2.3%). Fatal adverse reactions occurred in 1.1% patients who received NELKARMI, including cardiac arrest (0.3%), pulmonary embolism (0.2%), sudden death (0.2%), pneumonia (0.2%), aspiration pneumonia (0.2%), and shock hemorrhagic (0.2%).

Permanent discontinuation of NELKARMI due to adverse reactions occurred in 5% of patients. The most frequent adverse reactions that led to permanent discontinuation of NELKARMI in ≥2% was hepatotoxicity.

Dose reductions of NELKARMI due to an adverse reaction occurred in 17% of patients. The most frequent adverse reactions that led to dose reductions in ≥2% was hepatotoxicity.

Dosage interruptions of NELKARMI due to an adverse reaction occurred in 44% of patients. The most frequent adverse reactions that led to dose interruptions in ≥2% were hepatotoxicity, pneumonia, peripheral neuropathy, rash, and increased creatine phosphokinase.

Table 3 summarizes the adverse reactions that occurred in the ALKOVE-1 trial.

Table 3: Adverse Reactions (≥10%) in Patients With ALK-Positive NSCLC Who Received NELKARMI in ALKOVE-1

Adverse Reaction[1]	**NELKARMI N=656**	
	All Grades (%)	**Grade 3 or 4 (%)**
Hepatobiliary Disorders		
Hepatotoxicity[2]	57	25
Gastrointestinal Disorders		

Adverse Reaction[1]	NELKARMI N=656	
	All Grades (%)	Grade 3 or 4 (%)
Constipation	28	0.2
Nausea	16	0.8
Abdominal pain[2]	10	0.8
Nervous System Disorders		
Dysgeusia[2]	25	0
Peripheral neuropathy[2]	23	0.9
CNS effects[2]	18	1.2
Dizziness[2]	12	0.5
Headache[2]	12	0.5
General Disorders and Administration Site Conditions		
Fatigue[2]	21	0.9
Edema[2]	20	0.3
Respiratory Thoracic and Mediastinal Disorders		
Cough[2]	19	0.5
Dyspnea[2]	14	2.7
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[2]	33	1.5
Eye Disorders		
Ocular toxicity[2]	15	0.5
Skin and Subcutaneous Tissue Disorders		
Rash[2]	12	1.2

[1]Based on NCI CTCAE v5.0
[2] Grouped Terms

Clinically relevant adverse reactions in < 10% of patients who received NELKARMI included pneumonia, urinary tract infection, and QT prolongation.

Table 4 summarizes the laboratory abnormalities that occurred in ALKOVE-1.

Table 4: Select Laboratory Abnormalities (≥20%) That Worsened From Baseline in Patients With ALK-Positive NSCLC Who Received NELKARMI in ALKOVE-1

Laboratory Abnormality[1]	NELKARMI[2] N=656	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Eosinophils increased	33	0
Chemistry		
Aspartate aminotransferase increased	63	14
Alanine aminotransferase increased	63	18
Alkaline phosphatase increased	41	0.3
Creatine phosphokinase increased	29	4
Creatinine increased	25	0.5
Albumin decreased	24	0.5
Potassium increased	22	0.9
Calcium increased	20	0.3
Lipid Profile		
Cholesterol increased	45	1.3
Triglycerides increased	25	1

[1]Based on NCI CTCAE v5.0

[2]The denominator used to calculate the rate varied from 527 to 651 based on the number of patients with a baseline value and at least one post-baseline treatment value.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on NELKARMI

Strong and Moderate CYP3A Inhibitors

Avoid concomitant use of NELKARMI with strong or moderate CYP3A inhibitors.

Neladalkib is a CYP3A substrate. Concomitant use with a strong or moderate CYP3A inhibitor may increase neladalkib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of NELKARMI-associated adverse reactions.

Strong and Moderate CYP3A Inducers

Avoid concomitant use of NELKARMI with strong or moderate CYP3A inducers.

Concomitant use of NELKARMI with a strong or moderate CYP3A inducer may decrease neladalkib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may decrease the effectiveness of NELKARMI.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on literature reports in humans with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action *[see Clinical Pharmacology (12.1)]*, NELKARMI can cause fetal harm when administered to a pregnant woman. There are no available data on NELKARMI use in pregnant women to inform a drug-associated risk. Oral administration of neladalkib to pregnant rats during the period of organogenesis resulted in embryo-fetal mortality, alterations to growth, and structural abnormalities at maternal exposures ≥ 0.7 times the human exposure at the recommended dose based on AUC (*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

Human Data

Published reports of individuals with congenital mutations in TRK pathway proteins suggest that decreases in TRK mediated signaling are correlated with obesity, developmental delays, cognitive impairment, insensitivity to pain, and anhidrosis.

Animal Data

In an embryo-fetal development study, pregnant rats received oral doses of 2, 8, or 20 mg/kg/day of neladalkib during the period of organogenesis (gestation day 6 to 17). Neladalkib caused decreased fetal body weight and an increased incidence of skeletal variations (misshapen sternebra and cervical arch, incomplete ossification, and unossified sternebra) at doses ≥ 2 mg/kg/day (≥ 0.7 times the human exposure at the recommended dose based on AUC). Neladalkib also caused malformation (absent left kidney), post-implantation loss, and reduced number of fetuses at ≥ 8 mg/kg/day (≥ 3 times the human exposure at the recommended dose based on AUC).

8.2 Lactation

Risk Summary

There are no data on the presence of NELKARMI or its metabolites in human milk or its effects on a breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children from

NELKARMI, advise women not to breastfeed during treatment with NELKARMI and for 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

Females

Advise females of reproductive potential to use effective nonhormonal contraception during treatment with NELKARMI and for 2 weeks after the last dose. The effect of NELKARMI on hormonal contraception is unknown.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with NELKARMI and for 2 weeks after the last dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

Based on findings from animal studies, NELKARMI may impair fertility in males *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

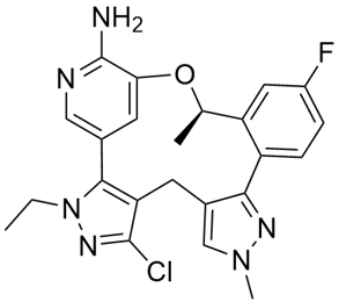
The safety and effectiveness of NELKARMI in pediatric patients have not been established.

8.5 Geriatric Use

Of the 700 patients who received NELKARMI, 18.0% were 65 to 75 years old, and 5.4% were older than 75 years of age. There were no clinically meaningful differences in safety and efficacy between patients younger than 65 years of age and patients 65 years of age or older.

11 DESCRIPTION

Neladalkib is a kinase inhibitor. The molecular formula for neladalkib is $C_{23}H_{22}ClFN_6O$ and the molecular weight is 452.92 Daltons. The chemical name is (*R*)-9-chloro-11-ethyl-21-fluoro-4-methyl-19-methyl-18-oxa-3,4,10,11,15-pentaazapentacyclo-[18.3.1.1^{13,17}.0^{2,6}.0^{8,12}] pentacosa-1(23),2,5,8(12),9,13,15,17(25),20(24),21-decaen-16-ylamine. The chemical structure of neladalkib is as follows:



Neladalkib is a white to tan powder with a pKa of 4.50 ± 0.07. The aqueous solubility of neladalkib at 37°C is pH dependent, decreasing from 29.6 mg/mL at pH 2.1 to less than 0.01 mg/mL at pH 6.8. The log of the distribution coefficient (octanol/water) at pH 7.4 is 3.72 ± 0.02.

NELKARMI (neladalkib) tablets for oral use are supplied as 50 mg and 150 mg dosage strengths. NELKARMI tablets, 50 mg are film-coated, oblong, orange tablets, debossed with “50” on one side and “NLD” on the other side of the tablet. NELKARMI tablets, 150 mg are film-coated, oblong, red tablets, debossed with “150” on one side and “NLD” on the other side of the tablet. Inactive ingredients in the tablet core are colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, and microcrystalline cellulose.

The 50 mg tablet orange film coating contains the inactive ingredients iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The 150 mg tablet red film coating contains the inactive ingredients iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Neladalkib is an inhibitor of tyrosine kinase ALK, including ALK resistance mutations. In vitro, neladalkib inhibited the viability of cultured cells expressing ALK alterations, including *ALK* fusions and *ALK* kinase domain single and compound mutations. In a biochemical assay, neladalkib inhibited ALK (IC_{50} = 0.9 nM) and also showed inhibitory effects on ROS1 (IC_{50} = 1.1 nM) and tropomyosin receptor kinases (TRKs), TRKB (IC_{50} = 26 nM), TRKC (IC_{50} = 96 nM), and TRKA (IC_{50} = 155 nM).

In mice subcutaneously implanted with tumors harboring *ALK* fusions and *ALK* single and compound mutations, including the G1202R, I1171N, G1202R/L1196M, or G1202R/G1269A mutations, administration of neladalkib resulted in tumor growth inhibition. Neladalkib had antitumor activity in intracranial xenograft models expressing *ALK* fusions with G1202R single or compound mutations.

12.2 Pharmacodynamics

Exposure-Response Relationships

An increased incidence of increased AST and increased ALP was observed with higher neladalkib exposure. An increased incidence of increased blood cholesterol, paresthesia, dysgeusia, and peripheral sensory neuropathy was observed with higher metabolite M14 exposure.

The exposure-response relationship and time course of pharmacodynamic response for the effectiveness of neladalkib have not been fully characterized.

Cardiac Electrophysiology

The largest mean increase in QTc interval was 8.8 ms (upper confidence interval = 11.0 ms) on Cycle 2 Day 1 after administration of NELKARMI 150 mg once daily in patients with advanced ALK-positive NSCLC and other advanced ALK-positive solid tumors (n = 144). Among 408 patients receiving 100 mg QD or 150 mg QD, 0.7% patients had a maximum post-baseline QTcF > 500 ms and 0.7% patients had maximum QTcF changes from baseline > 60 ms.

12.3 Pharmacokinetics

Neladalkib pharmacokinetics were observed at steady state in patients with locally advanced or metastatic ALK-positive NSCLC at the approved recommended dosage and are presented as mean (CV%), unless otherwise specified.

Neladalkib maximum concentration (C_{max}) is 886 (52%) ng/mL and total systemic exposure (AUC) is 7,906 (32%) ng·h/mL. The active metabolite M14 C_{max} is 601 (24%) ng/mL and AUC is 10,781 (27%) ng·h/mL. Neladalkib and M14 C_{max} and AUC increase in a dose-proportional manner across the dose range of 25 mg (0.17 times the approved recommended dosage) to 150 mg. Neladalkib accumulation is approximately 2-fold for AUC and 1.5-fold for C_{max}. Steady state is reached within 15 days.

Absorption

Neladalkib absolute oral bioavailability is 52%. Neladalkib median (min, max) time to maximum plasma concentration (T_{max}) was 1.1 hours (0.5, 6.2 hours) after a single dose.

Effect of Food

No clinically significant differences in neladalkib pharmacokinetics were observed following administration of a high fat meal (1000 calories, 60% fat).

Distribution

Neladalkib apparent volume of distribution is 628 L (36%). Neladalkib plasma protein binding is 98%. The blood to plasma ratio is 0.87.

Elimination

Neladalkib elimination half-life is 26 hours (18%) with a clearance of 19 L/h (32%). M14 elimination half-life is 49 hours (16%).

Metabolism

Neladalkib is primarily metabolized by CYP3A4 and to a lesser extent by CYP2C8 and CYP2C9. An active neladalkib metabolite, a des-ethyl metabolite (M14), that is less potent than the parent was identified in plasma, and its AUC represents 1.4-fold of the parent AUC.

Excretion

Following a single dose of radiolabeled neladalkib 150 mg, 72% of the dose was recovered in the feces (3% unchanged) and 15% in urine (0% unchanged).

Specific Populations

No clinically significant differences in the pharmacokinetics of neladalkib were observed based on age (19 to 83 years), sex, race (50% White, 26% Asian, and 2.6% Black), body weight (40 to 148 kg), eGFR 30 to < 90 mL/min, or mild (total bilirubin >1 to 1.5 times ULN or AST > ULN) to moderate (total bilirubin >1.5 to 3 times ULN with any AST) hepatic impairment. The effect of severe hepatic impairment (total bilirubin >3 times ULN with any AST), eGFR < 30 mL/min, or dialysis on neladalkib pharmacokinetics has not been studied.

Drug Interaction Studies

Clinical Studies

No clinically significant differences in neladalkib pharmacokinetics were observed when used concomitantly with lansoprazole (proton pump inhibitor).

In vitro studies

CYP450 Enzymes: Neladalkib is a reversible inhibitor of CYP2C8 and CYP3A4 and a time-dependent inhibitor of CYP3A, but not an inhibitor of CYP1A2, CYP2B6, CYP2C9, CYP2C19 or CYP2D6. M14 is a reversible and time-dependent inhibitor of CYP3A4, but not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6.

Neladalkib and M14 induce CYP3A.

UDP-glucuronosyltransferase (UGT): Neladalkib and M14 inhibit UGT1A1, UGT1A4, and UGT1A9, but do not inhibit UGT1A3, UGT1A6, UGT2B7 or UGT2B15.

Transporter Systems: Neladalkib is not a substrate of P-gp, BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1 and MATE2K. Neladalkib inhibits P-gp, BCRP, OATP1B1, OATP1B3, and MATE1, but does not inhibit OAT1, OAT3, OCT2 or MATE2K. M14 inhibits P-gp, BCRP, OATP1B1, OATP1B3, MATE1, and MATE2K, but does not inhibit OAT1, OAT3, OCT1, or OCT2.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies with neladalkib were not conducted.

Mutagenesis

Neladalkib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay or clastogenic in an in vitro assay in human lymphoblastoid TK6 cells. Neladalkib was not genotoxic in an in vivo micronucleus assay in rats.

Impairment of Fertility

Dedicated fertility studies were not conducted with neladalkib. In 4-week repeat dose toxicity studies with oral administration of neladalkib in dogs, adverse effects in male reproductive organs included degeneration and vacuolation of the testis and reversible epithelial atrophy and vacuolation in the epididymis at doses ≥2 mg/kg/day (≥3 times the human exposure at the recommended dose based on AUC). The testis findings were reversible at 2 mg/kg/day, whereas reversibility was not assessed at 6 mg/kg/day.

14 CLINICAL STUDIES

14.1 ALK-Positive Locally Advanced or Metastatic NSCLC Previously Treated with an ALK Kinase Inhibitor

The efficacy of NELKARMI was evaluated in patients with locally advanced or metastatic ALK-positive NSCLC previously treated with one or more ALK kinase inhibitors with or without prior platinum-based chemotherapy in the unresectable locally advanced or metastatic setting who received NELKARMI at a dose of 150 mg orally once daily in ALKOVE-1, a multicenter, single-arm, open-label, multi-cohort clinical trial (NCT05384626). Efficacy was evaluated in 67 patients who received 1 prior ALK TKI consisting of alectinib and 155 patients who received 2 or more prior ALK TKIs and prior platinum-based chemotherapy. Patients were required to have ALK-positive locally advanced or metastatic NSCLC, ECOG performance status ≤1, measurable disease per RECIST v1.1 and documented ALK rearrangement as determined in local laboratories by next-generation sequencing (NGS), polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH), or immunohistochemistry (IHC). Patients with tumors harboring additional activating molecular alterations were excluded.

The major efficacy outcome measures were confirmed overall response rate (ORR) and duration of response (DOR) according to RECIST v1.1 as assessed by blinded independent central review (BICR). Intracranial response according to modified RECIST v1.1 was assessed by BICR.

Among the 222 patients with ALK TKI-pretreated NSCLC, the median age was 56 years (range 23 to 83); 57% were female; 49% were White; 29% were Asian; 1.8% were Black or African American; 19% were unknown or other races and 0.5% were Native Hawaiian or Other Pacific Islander; and 5% were of Hispanic or Latino ethnicity. All patients had locally advanced or metastatic disease; 63% never smoked; 41% had CNS metastases by BICR; 97% had adenocarcinoma; 77% patients had received prior platinum-based chemotherapy. Among patients who received 2 or more prior ALK TKIs and prior platinum chemotherapy, 95% received lorlatinib, 88% received alectinib, 38% received crizotinib, 31% received brigatinib, 14% received ceritinib, 1.9% received ensartinib, 0.6% received an investigational TKI; 84% received both lorlatinib and alectinib.

Efficacy results are summarized in Table 5.

Table 5: Efficacy Results in ALKOVE-1 per BICR Assessment

Efficacy Parameters	1 prior ALK TKI consisting of alectinib (N=67)	2 or more prior ALK TKIs and prior platinum-based chemotherapy (N=155)
Overall Response Rate, % (95% CI)	49% (37, 62)	32% (24, 40)

Efficacy Parameters	1 prior ALK TKI consisting of alectinib (N=67)	2 or more prior ALK TKIs and prior platinum-based chemotherapy (N=155)
Complete Response	7%	3.9%
Partial Response	42%	28%
Duration of Response		
Median in Months (95% CI) [a]	NE (NE, NE)	17.3 (8.9, NE)
Range (months)	1.4+, 27.9+	3.0, 30.1+
Response Duration ≥6 months [b]	76%	69%
Response Duration ≥12 months [b]	52%	51%

Abbreviations: CI= confidence interval; NE= not evaluable

[a] Kaplan-Meier estimates

[b] Based on observed duration of response

+ Denotes censored value

In the 20 patients who had received 1 prior ALK TKI consisting of alectinib, measurable CNS metastases at baseline as assessed by BICR and had not received radiation therapy to the brain within 2 months prior to study entry; intracranial tumor responses were observed in 55% (95% CI: 32, 77) of patients including 25% of patients with a complete response.

In the 53 patients who had received 2 or more prior ALK TKIs and prior platinum-based chemotherapy, measurable CNS metastases at baseline as assessed by BICR and had not received radiation therapy to the brain within 2 months prior to study entry; intracranial tumor responses were observed in 26% (95% CI: 15, 40) of patients including 11% of patients with a complete response.

In the subset of patients who received 1 prior ALK TKI consisting of alectinib, there were 13 patients with ALK G1202R (ORR: 77% [95% CI: 46, 95]). In the subset of patients who received 2 or more prior ALK TKIs and platinum-based chemotherapy, there were 35 patients with ALK G1202R (ORR: 71% [95% CI: 54, 85]); 16 of these responders had ALK G1202R with additional ALK mutations, including compound mutations. Responses were also observed in patients with other mutations (C1156Y, I1171N, I1171T, F1174C, F1174I, F1174L, V1180L, L1196M, L1198F, D1203N, S1206F, E1210K, and G1269A).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied:

NELKARMI (neladalkib) tablets are supplied as follows:

Strength	Description	Package Configuration	NDC
50 mg	Orange oblong film-coated tablet, with “50” debossed on one side and “NLD” on the other side.	Bottle with child-resistant closure containing 30 tablets packaged in a carton.	85001-203-01
150 mg	Red oblong film-coated tablet, with “150” debossed on one side and “NLD” on the other side.	Bottle with child-resistant closure containing 30 tablets packaged in a carton.	85001-204-01

Storage and Handling:

Store NELKARMI at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Hepatotoxicity

Advise patients that NELKARMI can cause hepatotoxicity and to inform their healthcare provider if they experience signs or symptoms of hepatotoxicity. Advise patients of the need to monitor for ALT, AST, and total bilirubin elevations during treatment *[see Warnings and Precautions (5.1)]*.

Renal Toxicity

Advise patients that NELKARMI can cause renal toxicity and to inform their healthcare provider if they experience signs or symptoms of renal toxicity. Advise patients of the need to monitor renal function tests during treatment *[see Warnings and Precautions (5.2)]*.

Ocular Toxicity

Advise patients that NELKARMI can cause ocular toxicity and to inform their healthcare provider if they experience signs or symptoms of ocular toxicity. Advise patients of the need to monitor vision changes at regular intervals during treatment *[see Warnings and Precautions (5.3)]*.

Creatine Phosphokinase Elevation

Advise patients that NELKARMI can cause creatine phosphokinase (CPK) elevations and to inform their healthcare provider if they experience signs or symptoms of creatine phosphokinase elevation. Advise patients of the need to monitor CPK levels during treatment *[see Warnings and Precautions (5.4)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective nonhormonal contraception during treatment with NELKARMI and for 2 weeks after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with NELKARMI and for 2 weeks after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise females not to breastfeed during treatment with NELKARMI and for 2 weeks after the last dose *[see Use in Specific Populations (8.2)]*.

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions (7.1)]*.

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Version: 1, 11/2026

PATIENT INFORMATION
NELKARMI™ (nel-KAR-mee)
(neladalkib)
tablets, for oral use

What is NELKARMI?

NELKARMI is a prescription medicine used to treat adults with non-small cell lung cancer (NSCLC) that has spread to nearby tissue or lymph nodes (locally advanced) or other parts of the body (metastatic) and is caused by an abnormal anaplastic lymphoma kinase (ALK) gene.

NELKARMI may be right for you if you previously received the following treatment for unresectable locally advanced or metastatic disease:

- treatment with alectinib **or**
- 2 or more other prescription medicines specifically for ALK-positive NSCLC and platinum-containing chemotherapy.

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

Before taking NELKARMI, tell your healthcare provider about all your medical conditions, including if you:

- have liver problems
- have kidney problems
- have vision problems
- have muscle problems
- are pregnant or plan to become pregnant. NELKARMI can harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with NELKARMI.

  Females who are able to become pregnant:
  - Your healthcare provider will do a pregnancy test before you start treatment with NELKARMI.
  - Use effective nonhormonal birth control (contraception) during treatment with NELKARMI and for 2 weeks after the last dose of NELKARMI.
  - Talk to your healthcare provider about birth control methods that may be right for you.

  Males with female partners who are able to become pregnant:
  - Use effective birth control (contraception) during treatment with NELKARMI and for 2 weeks after the last dose.
- are breastfeeding or plan to breastfeed. It is not known if NELKARMI passes into your breast milk. **Do not** breastfeed during treatment with NELKARMI and for 2 weeks after the last dose of NELKARMI. Talk to your healthcare provider about the best way to feed your baby during treatment with NELKARMI.

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

NELKARMI may affect the way your other medicines work, and other medicines may affect the way NELKARMI works. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take NELKARMI?

- Take NELKARMI exactly as your healthcare provider tells you to take it. Do not change your dose or stop taking NELKARMI unless your healthcare provider tells you to.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with NELKARMI if you develop certain side effects.
- Take NELKARMI 1 time a day at the same time each day.
- Take NELKARMI with or without food.
- Swallow NELKARMI tablets whole. Do not split, chew, crush, or dissolve the tablets.
- If you miss a dose of NELKARMI for more than 12 hours, skip the missed dose. Take your next dose at your regular time.
- If you vomit after taking a dose of NELKARMI, do not take an extra dose. Take your next dose at your regular time.

What are the possible side effects of NELKARMI?

NELKARMI can cause serious side effects, including:

- **Liver Problems.** NELKARMI can cause severe liver problems that can be life-threatening. Your healthcare provider will do blood tests to check your liver before you start treatment with NELKARMI, every 2 weeks during the first 2 months of treatment, then monthly or more often as needed during your treatment. Tell your healthcare provider right away if you get any new or worsening signs or symptoms, including:
  - yellowing of your skin or the white part of your eyes
  - dark or brown (tea color) urine
  - bleed or bruise more easily than normal
  - itchy skin

- nausea or vomiting
- pain on the right side of your stomach area
- decreased appetite
- feeling tired

- **Kidney problems.** NELKARMI can cause severe kidney problems that can be life-threatening. Your healthcare provider will do blood tests to check your kidneys before you start treatment with NELKARMI, every 2 weeks during the first month of treatment, then from time to time as needed during your treatment. Tell your healthcare provider right away if you get a change in the amount or color of your urine, or if you get new or worsening swelling in your legs or feet.
- **Vision problems.** NELKARMI can cause vision problems. Your healthcare provider will check your eyes regularly for any changes in your vision during treatment with NELKARMI. Your healthcare provider may refer you to an eye specialist if you develop vision problems during treatment with NELKARMI. Tell your healthcare provider right away if you have any new vision problems, including:
  - decreased vision
  - blurred vision
  - eye irritation
  - eye pain
  - feeling like something is in your eyes
  - dry eyes
- **Muscle and joint pain.** NELKARMI can cause a severe increase in the level of an enzyme in your blood called creatine phosphokinase (CPK), which may be a sign of muscle damage. Your healthcare provider will do blood tests to check your CPK blood levels before you start treatment with NELKARMI, every 2 weeks during the first 2 months of treatment, then from time to time as needed during your treatment.

The most common side effects of NELKARMI include:

- liver problems
- muscle and joint pain
- constipation
- change in the way foods taste or loss of taste (dysgeusia)
- numbness, pain, tingling or burning in your hands or feet
- swelling of your hands, feet, face, or eyes
- tiredness (fatigue)

The most common severe abnormal blood tests of NELKARMI include:

- increased liver enzymes
- increased CPK
- decreased potassium
- decreased red blood cell counts
- decreased white blood cell counts

NELKARMI may cause fertility problems in males, which may affect your ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all of the possible side effects of NELKARMI.

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 NELKARMI?

- Store NELKARMI at room temperature between 68°F to 77°F (20°C to 25°C).
- The NELKARMI bottle has a child resistant cap closure.

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

General information about the safe and effective use of NELKARMI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use NELKARMI for a condition for which it was not prescribed. Do not give NELKARMI 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 NELKARMI that is written for health professionals.

What are the ingredients in NELKARMI?

Active ingredient: neladalkib

Inactive ingredients:
Tablet core: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, and microcrystalline cellulose.
Tablet coating: iron oxide red, iron oxide yellow (50 mg only), polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

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NELKARMI ™ is a trademark of Nuvalent, Inc. For more information, go to **www. NELKARMI.com** or call **1-844-NUVL-111** (1-844-688-5111).
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