

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218171Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ENSACOVE™ (ensartinib) capsules, for oral use

Initial U.S. Approval: 2024

INDICATIONS AND USAGE

ENSACOVE is a kinase inhibitor indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received an ALK-inhibitor. (1, 2.1)

DOSAGE AND ADMINISTRATION

- Select patients with ALK-positive locally advanced or metastatic NSCLC for treatment with ENSACOVE. (2.1)
- Prior to initiating ENSACOVE, evaluate liver function tests and fasting blood glucose. (2.2)
- **Recommended dosage:** 225 mg orally once daily with or without food until disease progression or unacceptable toxicity. (2.3)

DOSAGE FORMS AND STRENGTHS

Capsules: 25 mg and 100 mg of ensartinib (3)

CONTRAINDICATIONS

Hypersensitivity reaction to ENSACOVE, FD&C Yellow No. 5 (tartrazine), or to any of its components. (4)

WARNINGS AND PRECAUTIONS

- **Interstitial Lung Disease (ILD)/Pneumonitis:** Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis. Permanently discontinue in patients with ILD/pneumonitis. (5.1)
- **Hepatotoxicity:** Monitor liver function tests during treatment with ENSACOVE. Withhold, reduce the dose, or permanently discontinue ENSACOVE based on severity. (5.2)
- **Dermatologic Adverse Reaction:** Monitor for dermatologic adverse reactions during treatment with ENSACOVE. Withhold, reduce the dose, or permanently discontinue ENSACOVE based on severity. (5.3)
- **Bradycardia:** Monitor heart rate regularly during treatment with ENSACOVE. Withhold, reduce the dose, or permanently discontinue ENSACOVE based on severity. (5.4)
- **Hyperglycemia:** Monitor serum glucose periodically during treatment with ENSACOVE. Withhold, reduce the dose, or permanently discontinue ENSACOVE based on severity. (5.5)

- **Visual Disturbances:** Advise patients to report visual symptoms during treatment with ENSACOVE. Withhold ENSACOVE and obtain ophthalmologic evaluation, then reduce the dose or permanently discontinue ENSACOVE. (5.6)
- **Increased Creatine Phosphokinase (CPK):** Monitor CPK periodically during treatment with ENSACOVE. Withhold, reduce the dose, or permanently discontinue ENSACOVE based on severity. (5.7)
- **Hyperuricemia:** Monitor uric acid periodically during treatment with ENSACOVE. Withhold, reduce the dose, or permanently discontinue ENSACOVE based on severity. (5.8)
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception. (5.9)

ADVERSE REACTIONS

- Most common adverse reactions (incidence $\geq 20\%$) were rash, musculoskeletal pain, constipation, pruritus, cough, nausea, edema, vomiting, fatigue, and pyrexia. (6.1)
- Most common Grade 3-4 laboratory abnormality (incidence $\geq 2\%$) were increased uric acid, decreased lymphocytes, increased alanine aminotransferase, decreased phosphate, increased gamma glutamyl transferase, increased magnesium, increased amylase, decreased sodium, increased glucose, decreased hemoglobin, increased bilirubin, decreased potassium, and increased creatine phosphokinase. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Xcovery Holdings, Inc. at (866) 367-2268 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Moderate or Strong CYP3A Inhibitors:** Avoid concomitant use with ENSACOVE. (7.1)
- **Moderate or Strong CYP3A Inducers:** Avoid concomitant use with ENSACOVE. (7.1)
- **P-gp Inhibitor:** Avoid concomitant use with ENSACOVE. (7.1)

USE IN SPECIFIC POPULATIONS

- **Lactation:** Advise not to breastfeed. (8.2)
- **Severe Hepatic Impairment:** Avoid use of ENSACOVE in patients with severe hepatic impairment. (8.6)

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

Revised: 12/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ENSACOVE is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received an ALK-inhibitor.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of locally advanced or metastatic NSCLC with ENSACOVE based on the presence of ALK rearrangement(s) in tumor specimens [*see Clinical Studies (14.1)*]. An FDA-approved test to detect ALK rearrangements for selecting patients for treatment with ENSACOVE is not currently available.

2.2 Recommended Testing and Advice Prior to Initiating ENSACOVE

Prior to initiating ENSACOVE, evaluate liver function tests [*see Warnings and Precautions (5.2)*] and fasting blood glucose [*see Warnings and Precautions (5.5)*].

2.3 Recommended Dosage

The recommended dosage of ENSACOVE is 225 mg orally once daily, with or without food [*see Clinical Pharmacology (12.3)*], until disease progression or unacceptable toxicity.

Swallow capsules whole, do not crush or chew. Do not open or dissolve the contents of the capsule. Take ENSACOVE at the same time each day.

Missed dose

If a dose is missed, then take the missed dose as soon as possible unless the next dose is due within 12 hours. Do not take 2 doses on the same day.

Vomiting

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

2.4 Dosage Modification for Adverse Reactions

The recommended dose reductions for adverse reactions are provided in Table 1.

Table 1: Recommended Dose Reductions for Adverse Reactions

Dosage Reduction	Recommended Dose and Schedule
First	200 mg orally once daily
Second	150 mg orally once daily
Permanently discontinue ENSACOVE if patients are unable to tolerate 150 mg orally once daily.	

Once the dose has been reduced for adverse reactions, do not subsequently increase the dose of ENSACOVE.

The recommended dosage modifications for the management of adverse reactions are provided in Table 2.

Table 2: Recommended ENSACOVE Dosage Modifications and Management for Adverse Reactions

Adverse Reaction	Severity*	ENSACOVE Dose Modification and Management for Adverse Reactions
Interstitial Lung Disease (ILD)/Pneumonitis <i>[see Warnings and Precautions (5.1)]</i>	Any Grade	Permanently discontinue ENSACOVE.
Hepatotoxicity <i>[see Warnings and Precautions (5.2)]</i>	Grade 3 or 4 elevation (greater than 5 times ULN) of either ALT or AST with concurrent total bilirubin elevation less than or equal to 2 times ULN	- Withhold ENSACOVE until recovery to Grade ≤ 1 (≤ 3 times ULN) or to baseline. - Resume ENSACOVE at reduced dose as per Table 1.
	Grade 2 to 4 elevation (greater than 3 times ULN) of either ALT or AST with concurrent total bilirubin elevation greater than 2 times ULN in the absence of cholestasis or hemolysis	Permanently discontinue ENSACOVE.
Dermatologic Adverse Reactions <i>[see Warnings and Precautions (5.3)]</i>	Grade 1	Consider topical corticosteroids.
	Grade 2	- Administer topical corticosteroids. - If not improved in ≤ 7 days after initiation of topical corticosteroids, administer oral corticosteroids. - If not improved in ≤ 7 days after initiation of oral corticosteroids, withhold ENSACOVE until recovery to Grade ≤ 1.

Adverse Reaction	Severity*	ENSACOVE Dose Modification and Management for Adverse Reactions
		Resume ENSACOVE at reduced dose as per Table 1.
	Grade 3	- Withhold ENSACOVE. Administer topical corticosteroids. - If not improved after 7 days of initiation of topical corticosteroids, administer oral corticosteroids. - Resume ENSACOVE at reduced dose as per Table 1 upon improvement to Grade ≤ 1.
	Grade 4	- Permanently discontinue ENSACOVE. - Administer systemic corticosteroids and consider antibiotic use.
Bradycardia (HR less than 60 bpm) <i>[see Warnings and Precautions (5.4)]</i>	Symptomatic bradycardia	- Withhold ENSACOVE until recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. - If a concomitant medication known to cause bradycardia is identified and discontinued or dose-adjusted, resume ENSACOVE at same dose upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above. - If no concomitant medication known to cause bradycardia is identified, or if contributing concomitant medications are not discontinued or dose-adjusted, resume ENSACOVE at reduced dose as per Table 1 upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above.
	Bradycardia with life-threatening consequences, urgent intervention indicated	- Permanently discontinue ENSACOVE if no contributing concomitant medication is identified. - If contributing concomitant medication is identified and discontinued or dose-adjusted, resume ENSACOVE at reduced dose as per Table 1 upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above, with frequent monitoring as clinically indicated.

Adverse Reaction	Severity*	ENSACOVE Dose Modification and Management for Adverse Reactions
		For recurrence, permanently discontinue ENSACOVE.
Hyperglycemia [see Warnings and Precautions (5.5)]	Grade 3 (greater than 250 mg/dL) despite optimal anti-hyperglycemic therapy OR Grade 4	- Withhold ENSACOVE until hyperglycemia is adequately controlled, then resume ENSACOVE at reduced dose as per Table 1. - If adequate hyperglycemic control cannot be achieved with optimal medical management, permanently discontinue ENSACOVE.
Visual Disturbance [see Warnings and Precautions (5.6)]	Grade 2 or 3	Withhold ENSACOVE until recovery to Grade 1 or baseline, then consider resuming at reduced dose as per Table 1.
	Grade 4	Permanently discontinue ENSACOVE.
Increased Creatine Phosphokinase [see Warnings and Precautions (5.7)]	CPK elevation greater than 5 times ULN	Temporarily withhold ENSACOVE 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 ENSACOVE until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at reduced dose as per Table 1.
Hyperuricemia [see Warnings and Precautions (5.8)]	Symptomatic or Grade 4	- Initiate urate-lowering medication. - Withhold ENSACOVE until improvement of signs or symptoms. - Resume ENSACOVE at same or reduced dose.
Other Adverse Reactions [see Adverse Reactions (6.1)]	Grade 3 or 4	- Withhold ENSACOVE until recovery to Grade 1 or baseline. - Resume ENSACOVE at reduced dose as per Table 1.
	Recurrent Grade 4	Permanently discontinue ENSACOVE.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; bpm = beats per minute; HR = heart rate; ULN = upper limit of normal

*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.03.

3 DOSAGE FORMS AND STRENGTHS

ENSACOVE capsules are available as:

- 25 mg: size 2 capsule, white opaque cap and body, with “X-396” on the cap and “25 mg” on the body printed in blue ink. Each capsule contains the equivalent of 25 mg of ensartinib.

- 100 mg: size 0 capsule, blue opaque cap and yellow opaque body, with “X-396” on the cap and “100 mg” on the body printed in white ink. Each capsule contains the equivalent of 100 mg of ensartinib.

4 CONTRAINDICATIONS

ENSACOVE is contraindicated in patients who have experienced a severe hypersensitivity reaction to ENSACOVE, FD&C Yellow No. 5 (tartrazine), or to any of its components [*see Warnings and Precautions (5.10)*].

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease/Pneumonitis

ENSACOVE can cause severe interstitial lung disease (ILD)/pneumonitis.

In the pooled safety population [*see Adverse Reactions (6.1)*], ILD/pneumonitis occurred in 5% of patients treated with ENSACOVE, including Grade 3 in 1.3% and Grade 4 in 0.4%.

ILD/pneumonitis leading to dose interruption occurred in 0.4% and permanent discontinuation of ENSACOVE in 1.5% of patients.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, and fever) during treatment with ENSACOVE. Immediately withhold ENSACOVE in patients with suspected ILD/pneumonitis. Permanently discontinue ENSACOVE if ILD/pneumonitis is confirmed [*see Dosage and Administration (2.4)*].

5.2 Hepatotoxicity

ENSACOVE can cause hepatotoxicity including drug-induced liver injury.

In the pooled safety population [*see Adverse Reactions (6.1)*], 59% of patients treated with ENSACOVE had increased alanine aminotransferase (ALT), including 5% Grade 3. Increased aspartate aminotransferase (AST) occurred in 58% of patients treated with ENSACOVE, including 1.8% Grade 3. Increased bilirubin occurred in 12% of patients treated with ENSACOVE, including 2.3% Grade 3 and 0.2% Grade 4. There was one case of drug-induced liver injury in ENSACOVE-treated patients.

The median time to first onset of increased ALT or AST was 5.3 weeks (range: 0.4 to 152 weeks). The dose of ENSACOVE was interrupted in 4.6% of patients for increased ALT or AST. Increased ALT or AST leading to dose reduction occurred in 2.6% and permanent discontinuation of ENSACOVE in 1.1% of patients. The dose of ENSACOVE was interrupted in 1.3% of patients for increased bilirubin. Increased bilirubin leading to dose reduction occurred in 0.7% and permanent discontinuation of ENSACOVE in 1.3% of patients.

Monitor liver function tests including ALT, AST, and total bilirubin at baseline and every 2 weeks during the first cycle of treatment with ENSACOVE, and then monthly and as clinically indicated. Withhold, reduce the dose, or permanently discontinue ENSACOVE based on the severity of the adverse reaction [*see Dosage and Administration (2.4)*].

5.3 Dermatologic Adverse Reactions

ENSACOVE can cause dermatologic adverse reactions, including drug reaction with eosinophilia and systemic symptoms (DRESS), rash, pruritus, and photosensitivity.

In the pooled safety population [see *Adverse Reactions (6.1)*], dermatologic adverse reactions occurred in 80% of patients receiving ENSACOVE, including Grade 3 in 14% of patients. Rash occurred in 72% of patients receiving ENSACOVE, including Grade 3 in 12% of patients. The median time to onset of rash was 9 days (range: 1 day to 17.3 months). Pruritus occurred in 32% of patients receiving ENSACOVE, with Grade 3 in 2.4%. There was one Grade 3 case (0.2%) of drug reaction with eosinophilia and systemic symptoms (DRESS).

The dose of ENSACOVE was interrupted in 12% of patients for dermatologic adverse reactions. Dermatologic adverse reactions leading to dose reduction occurred in 11% and permanent discontinuation of ENSACOVE in 1.5% of patients.

In the pooled safety population [see *Adverse Reactions (6.1)*], photosensitivity occurred in 0.9% of patients receiving ENSACOVE; all were Grade 1.

Monitor patients for dermatologic adverse reactions during treatment with ENSACOVE. If dermatologic adverse reactions occur, treat with antihistamine, topical or systemic steroids based on the severity. Advise patients to limit direct sun exposure while taking ENSACOVE and for at least 1 week after discontinuation. Withhold, reduce the dose, or permanently discontinue ENSACOVE based on the severity of the adverse reaction [see *Dosage and Administration (2.4)*].

5.4 Bradycardia

ENSACOVE can cause symptomatic bradycardia.

In the pooled safety population [see *Adverse Reactions (6.1)*], bradycardia (heart rate less than 60 beats per minute) occurred in 6% of patients treated with ENSACOVE. All bradycardia events were Grade 1 or 2. Bradycardia requiring dose reduction occurred in 0.2% and led to dose interruption in 0.4% of ENSACOVE-treated patients.

Monitor heart rate regularly during treatment with ENSACOVE. Withhold, reduce the dose, or permanently discontinue ENSACOVE based on severity [see *Dosage and Administration (2.4)*].

5.5 Hyperglycemia

ENSACOVE can cause hyperglycemia.

In the pooled safety population [see *Adverse Reactions (6.1)*], based on laboratory data, 44% of patients receiving ENSACOVE experienced increased blood glucose, including Grade 3 in 2.5%. The median time to onset of increased blood glucose was 5.9 weeks (0.4 weeks to 3.4 years).

Assess fasting serum glucose at baseline and monitor serum glucose periodically during treatment with ENSACOVE. Withhold, reduce the dose, or permanently discontinue ENSACOVE based on severity [see *Dosage and Administration (2.4)*].

5.6 Visual Disturbances

ENSACOVE can cause visual disturbances including blurred vision, diplopia, photopsia, vitreous floaters, visual impairment, visual field defect, and reduced visual acuity.

In the pooled safety population [see *Adverse Reactions (6.1)*], 8% of patients receiving ENSACOVE experienced visual disturbance, including 0.2% Grade 3. Visual disturbances led to dose interruption in 0.4% of patients.

Obtain an ophthalmologic evaluation in patients with new or worsening visual symptoms during treatment with ENSACOVE. Withhold, reduce the dose, or permanently discontinue ENSACOVE based on severity [see *Dosage and Administration (2.4)*].

5.7 Increased Creatine Phosphokinase

In the pooled safety population [see *Adverse Reactions (6.1)*], of the 203 patients with creatine phosphokinase (CPK) laboratory data available, increased CPK occurred in 43% of patients who received ENSACOVE. The incidence of Grade 3 increased CPK was 1.5% and 0.5% were Grade 4. The median time to onset of increased CPK was 123 days (range: 13 days to 22 months). Increased CPK leading to dose interruption occurred in 0.2% and dose reduction in 0.4%.

Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels during treatment with ENSACOVE. Withhold, reduce the dose, or permanently discontinue ENSACOVE based on severity [see *Dosage and Administration (2.4)*, *Adverse Reactions (6.1)*].

5.8 Hyperuricemia

ENSACOVE can cause hyperuricemia.

In the pooled safety population [see *Adverse Reactions (6.1)*], based on adverse reactions, 6% of patients experienced hyperuricemia, with 0.4% Grade 3 and 0.7% Grade 4. Nine patients (1.9%) required hydration and two patients (0.4%) required urate-lowering medication.

Monitor serum uric acid levels prior to initiating ENSACOVE and periodically during treatment. Initiate treatment with urate-lowering medications as clinically indicated. Withhold, reduce the dose, or permanently discontinue ENSACOVE based on severity [see *Dosage and Administration (2.4)*].

5.9 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, ENSACOVE can cause fetal harm when administered to a pregnant woman. In embryo-fetal developmental studies, oral administration of ensartinib to pregnant rats during the period of organogenesis caused adverse developmental outcomes, including embryo-fetal mortality, alterations to growth, and structural abnormalities. Adverse embryo-fetal findings were seen at maternal exposures approximately equivalent to the human exposure at the recommended dose of 225 mg/day 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 contraception during treatment with ENSACOVE and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ENSACOVE and for 1 week after the last dose [see *Use in Specific Populations (8.1, 8.3)* and *Clinical Pharmacology (12.1)*].

5.10 FD&C Yellow No. 5 (Tartrazine)

This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of

FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

6 ADVERSE REACTIONS

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

- Interstitial Lung Disease/Pneumonitis [see *Warnings and Precautions* (5.1)]
- Hepatotoxicity [see *Warnings and Precautions* (5.2)]
- Dermatologic Adverse Reactions [see *Warnings and Precautions* (5.3)]
- Bradycardia [see *Warnings and Precautions* (5.4)]
- Hyperglycemia [see *Warnings and Precautions* (5.5)]
- Visual Disturbances [see *Warnings and Precautions* (5.6)]
- Increased Creatine Phosphokinase [see *Warnings and Precautions* (5.7)]
- Hyperuricemia [see *Warnings and Precautions* (5.8)]
- FD&C Yellow No. 5 (Tartrazine) [see *Warnings and Precautions* (5.10)]

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 reflects exposure to ENSACOVE as a single agent in 458 patients with locally advanced or metastatic ALK-positive NSCLC in the following trials: eXALT3 Study (N=143) [see *Clinical Studies* (14.1)], Study 101 (NCT01625234, N=98), Study BTP-28311 (NCT02959619, N=35), and Study BTP-42322 (NCT03215693, N=182). Patients received ENSACOVE 225 mg orally once daily, with or without food, until disease progression or unacceptable toxicity. Among 458 patients who received ENSACOVE, 63% were exposed for 6 months or longer and 47% were exposed for greater than one year. In this pooled safety population, the most common adverse reactions ($\geq 20\%$) were rash, musculoskeletal pain, constipation, pruritus, cough, nausea, edema, vomiting, fatigue, and pyrexia. The most frequent Grade 3 or 4 laboratory abnormalities ($\geq 2\%$) were increased uric acid, decreased lymphocytes, increased alanine aminotransferase, decreased phosphate, increased gamma glutamyl transferase, increased magnesium, increased amylase, decreased sodium, increased glucose, decreased hemoglobin, increased bilirubin, decreased potassium, and increased creatine phosphokinase.

TKI-naïve ALK-Positive Locally Advanced or Metastatic NSCLC

The safety of ENSACOVE was evaluated in the eXALT3 study [see *Clinical Studies* (14.1)]. Patients received ENSACOVE 225 mg orally once daily, with or without food, until disease progression or unacceptable toxicity. Among patients who received ENSACOVE, 78% were exposed for 6 months or longer and 66% were exposed for greater than one year.

The median age of patients who received ENSACOVE was 54 years (range: 25-86); 50% male; 54% Asian, 43% White; 0.7% Black or African American; and 11% Hispanic or Latino.

Serious adverse reactions occurred in 23% of patients treated with ENSACOVE. Serious adverse reactions that occurred in $\geq 1\%$ were pneumonia (4.9%), hemorrhage (2.1%), rash (2.1%) and cellulitis (1.4%). One fatal adverse reaction (0.7%) occurred due to bronchopneumonia.

Permanent discontinuation of ENSACOVE due to an adverse reaction occurred in 12% of patients. Adverse reactions which resulted in permanent discontinuation of ENSACOVE ($\geq 1\%$) included increased ALT (2.1%), increased AST (2.1%), pneumonitis/ILD (2.1%), increased blood bilirubin (1.4%), and increased conjugated bilirubin (1.4%).

Dose interruptions of ENSACOVE due to an adverse reaction occurred in 41% of patients. Adverse reactions which required dose interruptions ($\geq 2\%$) included rash (13%), increased ALT (6%), pneumonia (3.5%), edema (2.8%), pruritus (2.8%), pyrexia (2.8%), increased AST (2.1%), hemorrhage (2.1%), and decreased appetite (2.1%).

Dose reductions of ENSACOVE due to an adverse reaction occurred in 24% of patients. Adverse reactions which required dose reductions ($\geq 2\%$) included rash (11%), increased ALT (4.2%), pruritus (2.8%), and edema (2.1%).

Tables 3 and 4 summarize the most frequent adverse reactions and laboratory abnormalities, respectively.

Table 3: Adverse Reactions ($\geq 10\%$) in Patients with ALK-Positive Locally Advanced or Metastatic NSCLC Who Received ENSACOVE in eXALT3 Study

Adverse Reaction	ENSACOVE N = 143		Crizotinib N = 146	
	All Grades %	Grade 3 or 4 %	All Grades %	Grade 3 or 4 %
Skin and Subcutaneous Tissue Disorders				
Rash ^a	66	12	10	0
Pruritus ^b	30	2.1	4.1	0
Alopecia	11	0	4.8	0
Dry skin	10	0.7	0.7	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain ^c	36	1.4	20	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough ^d	31	0.7	16	0
Gastrointestinal Disorders				
Constipation	31	0	26	0
Nausea	28	1.4	30	2.1
Vomiting ^e	16	0.7	32	0
General Disorders and Administration Site Conditions				
Edema ^f	27	2.1	28	2.1
Pyrexia ^g	22	0.7	10	0.7
Fatigue ^h	21	0.7	14	1.4
Metabolism and Nutrition Disorders				
Decreased appetite	15	0	12	1.4
Infection and Infestation				
Respiratory Tract Infection	13	0.7	10	0

	ENSACOVE N = 143		Crizotinib N = 146	
Adverse Reaction	All Grades %	Grade 3 or 4 %	All Grades %	Grade 3 or 4 %
Nervous System Disorders				
Dizziness ⁱ	12	0.7	14	0.7
Dysgeusia	10	0	11	0
Vascular Disorders				
Hemorrhage ^j	10	1.4	4.8	0

Adverse reactions were graded using NCI CTCAE version 4.03.

^a Includes dermatitis, dermatitis acneiform, dermatitis bullous, drug eruption, eczema, exfoliative rash, palmar-plantar erythrodysesthesia, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic, rash pustular, skin exfoliation, and vulvovaginal rash

^b Includes ear pruritus, eye pruritus, eyelids pruritus, lip pruritus, pruritus, and pruritus generalized

^c Includes arthritis, spinal pain, myalgia, musculoskeletal pain, back pain, pain in extremity, neck pain, arthralgia, non-cardiac chest pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort

^d Includes cough, productive cough, upper-airway cough syndrome

^e Includes vomiting and retching

^f Includes eyelid edema, face edema, generalized edema, localized edema, edema, edema peripheral, gravitational edema, skin edema, eye edema, and periorbital edema.

^g Includes pyrexia and hyperthermia

^h Includes fatigue and asthenia.

ⁱ Includes dizziness, vertigo, postural dizziness

^j Includes hemoptysis, intracranial hemorrhage, gastrointestinal hemorrhage, hematuria, upper gastrointestinal hemorrhage, vaginal hemorrhage, gingival bleeding, vitreous hemorrhage, epistaxis, rectal hemorrhage, anal hemorrhage

Table 4: Select Laboratory Abnormalities (≥20%) That Worsened from Baseline in Patients with ALK-Positive Locally Advanced or Metastatic NSCLC Who Received ENSACOVE in eXALT3 Study

	ENSACOVE N = 143		Crizotinib N = 146	
Lab Abnormality	All Grades %	Grade 3 or 4 %	All Grades %	Grade 3 or 4 %
Chemistry				
Alanine aminotransferase increased	73	5	74	8
Alkaline phosphatase increased	64	2.2	50	0.7
Aspartate aminotransferase increased	64	1.4	62	3.5
Glucose increased	49	5	35	0.7
Albumin decreased	46	0.7	56	1.4
Phosphate decreased	39	7	42	4.9
Urate increased	39	39	27	27
Creatinine increased	37	0	27	0
Calcium decreased	36	1.4	64	4.9
Sodium decreased	27	4.3	27	4.2
Hematology				
Lymphocytes decreased	57	7	47	5
Hemoglobin decreased	43	0.7	31	1.4

Adverse reactions were graded using NCI CTCAE version 4.03.

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase

Clinically relevant adverse reactions in <10% of patients who received ENSACOVE included interstitial lung disease, photosensitivity, increased creatinine phosphokinase, bradycardia, and visual disturbances.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ENSACOVE

Table 5 describes drug interactions where concomitant use of another drug affects ENSACOVE.

Table 5: Effect of Other Drugs on ENSACOVE

Strong or Moderate CYP3A Inhibitors	
<i>Prevention or Management</i>	Avoid concomitant use of strong or moderate CYP3A inhibitors with ENSACOVE.
<i>Mechanism and Clinical Effect(s)</i>	This recommendation is based upon a mechanistic understanding of ensartinib pharmacokinetics and it being a CYP3A4 substrate in vitro [see <i>Clinical Pharmacology</i> (12.3)]. Concomitant use with strong or moderate CYP3A inhibitors may increase ensartinib exposure; however, this has not been studied clinically.
Strong or Moderate CYP3A Inducers	
<i>Prevention or Management</i>	Avoid concomitant use of strong or moderate CYP3A inducers with ENSACOVE.
<i>Mechanism and Clinical Effect(s)</i>	This recommendation is based upon a mechanistic understanding of ensartinib pharmacokinetics and it being a CYP3A4 substrate in vitro [see <i>Clinical Pharmacology</i> (12.3)]. Concomitant use with strong or moderate CYP3A inducers may decrease ensartinib exposure; however, this has not been studied clinically.
P-gp Inhibitors	
<i>Prevention or Management</i>	Avoid concomitant use of P-gp inhibitors with ENSACOVE.
<i>Mechanism and Clinical Effect(s)</i>	This recommendation is based upon a mechanistic understanding of ensartinib pharmacokinetics and it being a P-gp substrate in vitro [see <i>Clinical Pharmacology</i> (12.3)]. Concomitant use with P-gp inhibitors may increase ensartinib exposure; however, this has not been studied clinically.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Oral administration of ensartinib to pregnant rats during the period of organogenesis caused adverse developmental outcomes, including embryo-fetal mortality, alterations to growth, and structural abnormalities. Adverse embryo-fetal findings were seen at maternal exposures approximately equivalent to the human exposure at the recommended dose of 225 mg/day 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

Animal Data

In an embryo-fetal development study, pregnant rats received 20, 40, or 80 mg/kg/day of ensartinib during the period of organogenesis (gestation day 6 to 17). Ensartinib doses ≥ 40 mg/kg/day (approximately equivalent to the human exposure at the recommended dose of 225 mg/day based on AUC) resulted in an increase in the incidence of fetal malformations (aortic dislocation, ventricular septal defect, separated vertebrae) and dose-dependent delayed skeletal development, including decreased or delayed ossification of the vertebrae. Ensartinib at 80 mg/kg (approximately 6.4 times the human exposure at the recommended dose of 225 mg/day based on AUC) resulted in maternal toxicity (reduced body weight and food consumption), decreased fetal body weight, increased pre- and post-implantation loss, decreases in the number of live fetuses, and visceral variations (missing renal papillae, pyelectasis).

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

ENSACOVE 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 ENSACOVE.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with ENSACOVE and for at 1 week after the last dose.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENSACOVE and for 1 week after the last.

8.4 Pediatric Use

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

8.5 Geriatric Use

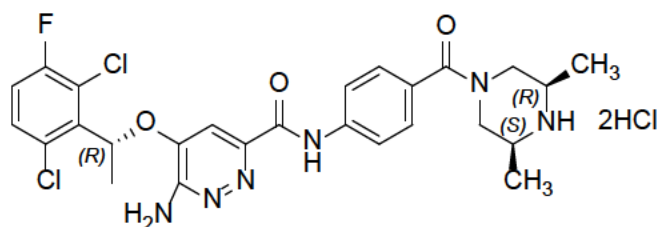
Of the 458 patients enrolled in clinical studies and received ENSACOVE 225 mg once daily, 16% of the participants were aged 65 years or older. Clinical studies of ENSACOVE did not include sufficient numbers of patients ages 65 and over to determine whether they respond differently from younger patients. Exploratory analysis suggests a higher incidence of serious adverse events (43% vs 27%), more frequent adverse events leading to treatment discontinuations (18% vs 10%) and dose modifications (34% vs 16%) in patients 65 years or older as compared to those younger than 65 years.

8.6 Hepatic Impairment

Ensartinib is primarily metabolized by the liver and patients with hepatic impairment may have increased exposures [see *Clinical Pharmacology* (12.3)]. Avoid use of ENSACOVE for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST) since it has not been studied in this population. Monitor patients with moderate hepatic impairment (total bilirubin >1.5 to ≤ 3 ULN and any AST) for increased adverse reactions and adjust ENSACOVE dosage as clinically indicated [see *Dosage and Administration* (2.4), *Warnings and Precautions* (5.2)]. No dosage modification is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and AST > ULN or total bilirubin 1 to 1.5 x ULN and any AST).

11 DESCRIPTION

ENSACOVE capsules contain ensartinib, a kinase inhibitor, present as ensartinib hydrochloride with the chemical name 6-amino-5-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-*N*-{4-[(3*R*,5*S*)-3,5-dimethylpiperazine-1-carbonyl]phenyl}pyridazine-3-carboxamide, dihydrochloride. The molecular formula is C₂₆H₂₇Cl₂FN₆O₃·2HCl and its molecular weight is 634.4 g/mol with the following structure:



ENSACOVE capsules are intended for oral administration and are available in two dosage strengths: 25 mg ensartinib (equivalent to 28.25 mg ensartinib hydrochloride) and 100 mg ensartinib (equivalent to 113.02 mg ensartinib hydrochloride).

The inactive ingredients of ENSACOVE capsules are microcrystalline cellulose and stearic acid. The inactive ingredients of the 25 mg empty capsule shells are hypromellose and titanium dioxide. The inactive ingredients of the 100 mg empty capsules shells are black iron oxide, FD&C Blue No. 1, FD&C Yellow No. 5, hypromellose, red iron oxide, and titanium dioxide.

The imprinting ink for the 25 mg capsules contains butyl alcohol, dehydrated alcohol, FD&C Blue No. 2, isopropyl alcohol, propylene glycol, shellac, and strong ammonia solution. The imprinting ink for the 100 mg capsules contains butyl alcohol, dehydrated alcohol, isopropyl alcohol, povidone, propylene glycol, shellac, sodium hydroxide, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ensartinib is a kinase inhibitor of anaplastic lymphoma kinase (ALK) and inhibits other kinases including MET and ROS1. In vitro, ensartinib inhibited phosphorylation of ALK and its downstream signaling proteins AKT, ERK, and S6, thereby blocking ALK-mediated signaling pathways and inhibiting proliferation in cell lines harboring ALK fusions and mutations. In vivo, ensartinib showed anti-tumor activity in a mouse xenograft model of human NSCLC harboring an ALK fusion.

12.2 Pharmacodynamics

Exposure-response relationship

Ensartinib exposure-response relationships and the time course of the pharmacodynamic response have not been fully characterized.

Cardiac Electrophysiology

At the approved recommended dosage, a mean increase in the QTc interval > 20 ms was not observed.

12.3 Pharmacokinetics

Ensartinib mean (coefficient of variation [CV%]) maximum concentration (C_{max}) is 292 ng/mL (60%), and the area under the concentration-time curve (AUC_{0-24h}) is 4,920 ng·h/mL (62%) at the approved recommended dosage. Ensartinib steady state is reached within 15 days with a mean accumulation ratio of 2.7.

Absorption

Ensartinib median (minimum, maximum) time to reach C_{max} (T_{max}) at steady state is 3 hours (2, 8 hours).

Effect of Food

No clinically significant differences in ensartinib pharmacokinetics were observed following administration of ENSACOVE with a high-fat meal (total 800-1000 calories, > 50% fat) compared to fasted conditions.

Distribution

Ensartinib mean (CV%) apparent volume of distribution is 1,720 L (42%). Ensartinib is 91.6% bound to human plasma protein.

Elimination

Ensartinib mean (standard deviation [SD]) steady-state half-life ($t_{1/2}$) is 30 (20) hours.

Metabolism

Ensartinib is predominantly metabolized by CYP3A.

Excretion

Following a single oral 200 mg dose of radiolabeled ensartinib, 91% of the radioactivity was recovered in feces (38% as unchanged) and 10% in urine (4.4% as unchanged).

Specific Populations

No clinically significant differences in the pharmacokinetics of ensartinib were observed based on age (20 to 86 years), sex, race (Asian vs White), body weight (38 to 148 kg), mild to moderate renal impairment (eGFR 30 to 89 mL/min) and mild hepatic impairment (total bilirubin $\leq$ upper limit of normal (ULN) and AST $>$ ULN or total bilirubin 1 to 1.5 x ULN and any AST).

The effect of severe renal impairment (eGFR 15 to 29 mL/min), end-stage renal disease (eGFR <15 mL/min) with or without hemodialysis, and moderate (total bilirubin >1.5 to ≤ 3 ULN and any AST) or severe (total bilirubin >3 times ULN and any AST) hepatic impairment on ensartinib pharmacokinetics is unknown.

Drug Interaction Studies

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Ensartinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and does not induce CYP1A2, CYP2B6, or CYP3A.

Transporter Systems: Ensartinib is a P-gp substrate but is not a substrate of BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2.

Ensartinib does not inhibit BCRP, P-gp, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2 or OCT3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ensartinib.

Ensartinib was not mutagenic in a bacterial reverse mutation (Ames) assay and was not clastogenic in an in vitro human lymphocyte chromosome aberration assay or an in vivo rat bone marrow micronucleus assay.

Dedicated fertility studies were not conducted with ensartinib. No adverse effects on male or female reproductive organs were observed in up to 3-month repeat-dose toxicology studies conducted in rats and dogs.

14 CLINICAL STUDIES

14.1 TKI-naïve ALK-Positive Locally Advanced or Metastatic NSCLC (eXALT3 Study)

The efficacy of ENSACOVE was evaluated in the eXALT3 study (NCT02767804), an open-label, randomized, active-controlled, multicenter study in adult patients with locally advanced (stage IIIB following prior chemotherapy or chemoradiation or not amenable to curative intent

therapy) or metastatic ALK-positive NSCLC. Patients were required to have ALK-positive NSCLC and an ECOG performance status of 0, 1, or 2. Patients could have received one prior regimen of chemotherapy but could not have previously received an ALK-targeted therapy. Patients with asymptomatic, untreated brain metastases who were not on corticosteroids and patients with asymptomatic, treated brain metastases who were on stable or decreasing dose of corticosteroids were eligible. Patients were required to have completed radiation therapy at least 2 weeks, or chemotherapy at least 4 weeks, prior to enrollment. Patients with leptomeningeal disease were ineligible.

Patients were randomized 1:1 to receive ENSACOVE 225 mg orally once daily or crizotinib 250 mg orally twice daily in 28-day cycles until disease progression or unacceptable toxicity. Randomization was stratified by prior chemotherapy (0 vs. 1), ECOG performance status (0 or 1 vs. 2), presence of central nervous system (CNS) metastases (yes or no), and geographic region (Asia vs. the rest of the world). Tumor assessments were performed every 8 weeks.

The main efficacy outcome measure was progression-free survival (PFS) as evaluated by Blinded Independent Central Review (BICR) according to RECIST version 1.1. The key secondary efficacy outcome measure was overall survival (OS); other secondary outcome measures included CNS response rate, time to CNS progression, and overall response rate (ORR).

A total of 290 patients were randomized to ENSACOVE (n=143) or crizotinib (n=147). The baseline demographic characteristics of the overall study population were median age 54 years (range: 25-90); 16% age > 65 years; 51% male; 56% Asian; 41% White and 1.4% Black; 8% Hispanic or Latino; ECOG PS 0 or 1 (95%); and 62% never smokers. Patients had Stage IIIB (8%) or Stage IV NSCLC (92%); 26% had received prior chemotherapy for advanced disease and 17% had received prior radiation. Baseline CNS metastases were present in 36% of the patients.

The eXALT3 study demonstrated a statistically significant improvement in PFS for patients randomized to ENSACOVE compared to patients randomized to crizotinib. The efficacy results as assessed by BICR are summarized in Table 6 and Figure 1.

Table 6: Efficacy Results for eXALT3 Study According to BICR Assessment

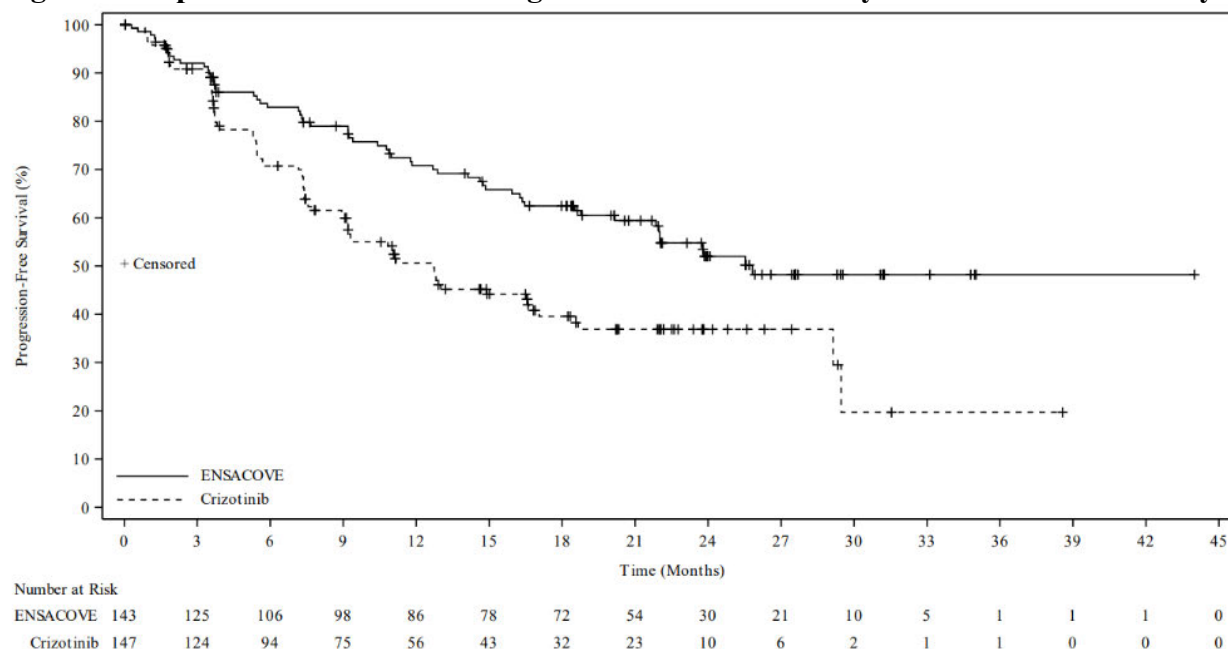
Efficacy Parameter	ENSACOVE N=143	Crizotinib N=147
Progression-free survival		
Number of events, n (%)	59 (41%)	80 (54%)
Progressive disease, n (%)	51 (36%)	77 (52%)
Death, n (%)	8 (6%)	3 (2%)
Median, months (95% CI)	25.8 (21.8, NE)	12.7 (9.2, 16.6)
Hazard ratio (95% CI)	0.56 (0.40, 0.79)	
p-value ^a	0.0007	
Overall response rate		
Overall response rate % (95% CI)	74% (66, 81)	67% (58, 74)
Complete response %	12%	5%
Partial response %	62%	61%

Efficacy Parameter	ENSACOVE N=143	Crizotinib N=147
Duration of response		
Number of responders, n	106	98
Median, months (95% CI)	NE (22.0, NE)	27.3 (12.9, NE)

CI = Confidence Interval; NE=not estimable; BICR = Blinded Independent Central Review

^a p-value based on unstratified log-rank test

Figure 1: Kaplan-Meier Curves of Progression-Free Survival by BICR in eXALT3 Study



At the time of the primary PFS analysis, OS results were immature. At the time of final analysis of OS, there was no statistically significant difference (p-value = 0.4570) between ENSACOVE and crizotinib. Median OS was 63.2 months in the ENSACOVE arm and 55.7 months in the crizotinib arm, with the hazard ratio of 0.88 (95% CI: 0.63, 1.23).

The results of the pre-specified analyses of CNS response rate by BICR in patients with baseline measurable CNS disease are summarized in Table 7.

Table 7: CNS ORR and DOR by BICR in Patients with Baseline Measurable CNS Disease in eXALT3 Study

Efficacy Parameter	ENSACOVE N=17	crizotinib N=24
CNS overall response rate % (95% CI)	59% (33, 82)	21% (7, 42)
Complete response %	24%	8%
Partial response %	35%	13%
Duration of Response		
Number of responders, n	10	5
Patients with DOR $\geq$ 12 months	30%	40%

BICR = Blinded Independent Central Review; CI = Confidence Interval

16 HOW SUPPLIED/STORAGE AND HANDLING

ENSACOVE (ensartinib) capsules are supplied as follows:

Capsule Strength	Description	Package Configuration	NDC Code
25 mg	Size 2 capsule, white opaque cap and body, with “X-396” on the cap and “25 mg” on the body printed in blue ink.	Bottles of 30	83076-1025-3
100 mg	Size 0 capsule, blue opaque cap and yellow opaque body, with “X-396” on the cap and “100 mg” on the body printed in white ink.	Bottles of 60	83076-1100-6

Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store and dispense in the original bottle with desiccant to protect from moisture. Do not remove desiccant from bottle. Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

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

Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the risk of severe ILD/pneumonitis during treatment with ENSACOVE. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms [see Warnings and Precautions (5.1)].

Hepatotoxicity

Inform patients of the potential risk of hepatotoxicity during treatment with ENSACOVE and of the need to monitor for aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin elevations during treatment with ENSACOVE. Advise patients to inform their healthcare provider of any new or worsening symptoms [see Warnings and Precautions (5.2)].

Dermatologic Adverse Reactions

Inform patients of the potential risk of dermatologic adverse reactions, including rash, pruritus, and photosensitivity during treatment with ENSACOVE. If dermatologic reactions occur, advise patients to limit sun exposure while taking ENSACOVE and for at least 1 week after the final dose [see Warnings and Precautions (5.3)].

Bradycardia

Advise patients of the risk of bradycardia during treatment with ENSACOVE and to report any symptoms of bradycardia. Advise patients to inform their healthcare provider about the use of

any heart or blood pressure medications during treatment with ENSACOVE [see *Warnings and Precautions* (5.4)].

Hyperglycemia

Inform patients of the risks of new or worsening hyperglycemia during treatment with ENSACOVE and the need to periodically monitor glucose levels. Advise patients with diabetes mellitus or glucose intolerance that antihyperglycemic medications may need to be adjusted during treatment with ENSACOVE [see *Warnings and Precautions* (5.5)].

Visual Disturbances

Advise patients to inform their healthcare provider of any new or worsening vision symptoms during treatment with ENSACOVE [see *Warnings and Precautions* (5.6)].

Creatine Phosphokinase (CPK) Elevation

Inform patients of the signs and symptoms of creatine phosphokinase (CPK) elevation and the need for monitoring during treatment with ENSACOVE. Advise patients to inform their healthcare provider of any new or worsening symptoms [see *Warnings and Precautions* (5.7)].

Hyperuricemia

Inform patients of the signs and symptoms of hyperuricemia. Advise patients to inform their healthcare provider if they experience signs or symptoms associated with hyperuricemia during treatment with ENSACOVE [see *Warnings and Precautions* (5.8)].

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy. Advise females of reproductive potential to use effective contraception during treatment with ENSACOVE and for 1 week after the last dose [see *Warnings and Precautions* (5.9) and *Use in Specific Populations* (8.1, 8.3)].

Advise males with female partners of reproductive potential to use effective contraception during treatment with ENSACOVE and for 1 week after the last dose [See *Warnings and Precautions* (5.9) and *Use in Specific Populations* (8.3)].

FD&C Yellow No. 5 (tartrazine)

Advise patients that this product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type or asthma-type reactions in certain susceptible persons (e.g., patients who also have aspirin hypersensitivity) [see *Warnings and Precautions* (5.10)]. Advise patients to contact their healthcare provider and seek medical help right away if they develop symptoms of an allergic reaction to FD&C Yellow No. 5 (tartrazine).

Lactation

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

Administration

Instruct patients to take ENSACOVE once a day with or without food and to swallow ENSACOVE capsules whole [see *Dosage and Administration* (2.2)].

Missed Dose

Advise patients to take ENSACOVE at the same time each day. If a dose is missed, then they should take the missed dose as soon as possible unless the next dose is due within 12 hours.

Patients should be instructed not to take 2 doses at the same time to make up for a missed dose.

In addition, instruct patients not to take an extra dose if they vomit after taking ENSACOVE [*see Dosage and Administration (2.2)*].

Manufactured for: Xcovery Holdings, Inc. Miami, FL 33131

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PATIENT INFORMATION
ENSACOVE™ (En-sa-kowv)
(ensartinib)
capsules, for oral use

What is ENSACOVE?

ENSACOVE 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,
- that has spread to other parts of your body, and
- who have not received medicines called ALK-inhibitors.

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

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

Do not use ENSACOVE if you are allergic to ENSACOVE, FD&C No. 5 (tartrazine), or to any of the ingredients in ENSACOVE. See the end of this leaflet for a complete list of ingredients in ENSACOVE.

Before using ENSACOVE, tell your healthcare provider about all of your medical conditions, including if you:

- have lung or breathing problems
- have liver problems
- have problems with your heartbeat
- have diabetes mellitus or glucose intolerance
- have problems with your vision
- are pregnant or plan to become pregnant. ENSACOVE can harm your unborn baby.
 - Your healthcare provider will do a pregnancy test before you start treatment with ENSACOVE.
 - Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with ENSACOVE.
 - **Females** who are able to become pregnant should use effective birth control (contraception) during treatment with ENSACOVE and for 1 week after the last dose of ENSACOVE. Talk to your healthcare provider about birth control choices that are right for you during treatment with ENSACOVE.
 - **Males** who have female partners who are able to become pregnant should use effective birth control (contraception) during treatment with ENSACOVE and for 1 week after the last dose of ENSACOVE.
- are breastfeeding or plan to breastfeed. It is not known if ENSACOVE passes into your breast milk. Do not breastfeed during treatment with ENSACOVE and for 1 week after the last dose. Talk to your healthcare provider about the best way to feed your baby during this time.

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

Certain other medicines may affect the way that ENSACOVE works and may increase your risk of certain side effects. Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take ENSACOVE?

- Take ENSACOVE exactly as your healthcare provider tells you to take it. Do not change your dose or stop taking ENSACOVE unless your healthcare provider tells you to.
- Swallow ENSACOVE capsules whole. Do not crush or chew capsules. Do not open or dissolve the contents of the capsule.
- Take ENSACOVE 1 time a day, at the same time each day.
- You may take ENSACOVE with or without food.
- If you miss a dose, take it as soon as you remember. If your next dose is due within 12 hours, skip the missed dose and take your next dose at your regular time. **Do not** take 2 doses of ENSACOVE on the same day to make up for the missed dose.
- If you vomit after taking a dose of ENSACOVE, do not take an extra dose. Take your next dose at your regular time.

What should I avoid while taking ENSACOVE?

- Limit your time in the sun during treatment with ENSACOVE and for at least 1 week after your last dose. ENSACOVE may make your skin sensitive to sunlight. You may burn more easily and get severe sunburns. When you are in the sun, wear a hat and protective clothing, and use a broad-spectrum sunscreen and lip balm with a Sun Protection Factor (SPF) of 30 or greater to protect against sunburn.

What are the possible side effects of ENSACOVE?

ENSACOVE can cause serious side effects, including:

- **Lung problems.** ENSACOVE can cause severe or life-threatening swelling (inflammation) of the lungs. Symptoms may be similar to those from lung cancer. Tell your healthcare provider right away if you get any new or worsening symptoms of lung problems during treatment with ENSACOVE, including:
 - trouble breathing or shortness of breath
 - cough with or without mucus
 - chest pain
 - fever
- **Liver problems.** ENSACOVE can increase enzymes called aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and levels of bilirubin in your blood. Tell your healthcare provider if you get new or worsening signs or symptoms of liver problems, including:
 - yellowing of your skin or the white part of your eyes
 - bleed or bruise more easily than normal
 - dark or brown (tea color) urine
 - itchy skin
 - nausea or vomiting
 - decreased appetite
 - pain on the right side of your stomach area
 - feeling tired
- **Skin reactions.** ENSACOVE may cause skin reactions that require treatment. Tell your healthcare provider if you get symptoms of skin reactions, such as rash, itching, or skin swelling.
- **Slow heart rate (bradycardia).** ENSACOVE can cause very slow heartbeats that can be severe. Your healthcare provider will check your heart rate during treatment with ENSACOVE. Tell your healthcare provider right away if you feel dizzy, lightheaded, or faint during treatment with ENSACOVE. Tell your healthcare provider if you take any heart or blood pressure medicines.
- **High blood sugar (hyperglycemia).** ENSACOVE can increase your blood sugar levels. Hyperglycemia is common with ENSACOVE treatment but can be serious. If you take medicine for diabetes or glucose intolerance your healthcare provider may change your medicine during treatment with ENSACOVE. Tell your healthcare provider if you get new or worsening signs and symptoms of hyperglycemia, including:
 - feeling very thirsty
 - feeling sick to your stomach
 - needing to urinate more than usual
 - feeling weak or tired
 - feeling very hungry
 - feeling confused
- **Vision problems.** ENSACOVE can cause vision problems. Your healthcare provider may refer you to an eye specialist if you develop new or worsening vision problems during treatment with ENSACOVE. Tell your healthcare provider if you have any loss of vision or any change in vision, including:
 - blurry vision
 - light hurting eyes
 - double vision
 - new or increased floaters
 - seeing flashes of light
- **Muscle pain, tenderness, and weakness (myalgia).** ENSACOVE can increase the level of an enzyme in your blood called creatine phosphokinase (CPK), which may be a sign of muscle damage. Myalgia is common with ENSACOVE treatment but can be serious. Tell your healthcare provider 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.
- **Increased uric acid level in your blood (hyperuricemia).** ENSACOVE can cause too much uric acid in your blood. Hyperuricemia is common with ENSACOVE treatment but can be serious. Your healthcare provider may prescribe medicines if you have high blood uric acid levels. Tell your healthcare provider if you develop any of the following symptoms of hyperuricemia:
 - red, hot, tender, or swollen joints, especially your big toe
 - nausea or vomiting
 - pain in your stomach-area or sides
 - pink or brown urine
- **Allergic reactions to FD&C Yellow No. 5 (tartrazine).** ENSACOVE 100 mg capsules contain FD&C Yellow No. 5. FD&C Yellow No. 5 (tartrazine) that can cause allergic reactions in certain people, especially people who also have

an allergy to aspirin. Tell your healthcare provider if you get hives, rash, or trouble breathing during treatment with ENSACOVE.

Your healthcare provider will do certain blood tests before and during treatment with ENSACOVE to check you for side effects.

If you have serious side effects during treatment with ENSACOVE, your healthcare provider may change your dose, stop your treatment for a period of time (temporary), or completely stop treatment with ENSACOVE.

The most common side effects of ENSACOVE are:

- rash
- muscle or bone pain
- constipation
- itching
- coughing
- nausea
- skin swelling (edema)
- vomiting
- tiredness
- fever
- increased levels of liver and pancreatic enzymes
- decreased white blood cell counts
- changes in blood levels of phosphate, magnesium, sodium, and potassium
- decreased protein (hemoglobin) in red blood cells
- increased bilirubin blood levels

These are not all the possible side effects with ENSACOVE.

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 ENSACOVE?

- Store ENSACOVE at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep ENSACOVE capsules in the original bottle.
- The bottle of ENSACOVE capsules contains a drying agent (desiccant) to help keep your medicine dry. Do not remove the desiccant from the bottle after opening. Do not open or eat the desiccant.

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

General information about the safe and effective use of ENSACOVE.

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

What are the ingredients in ENSACOVE?

Active ingredient: ensartinib hydrochloride

Inactive ingredients: butyl alcohol, dehydrated alcohol, hypromellose, isopropyl alcohol, microcrystalline cellulose, propylene glycol, shellac, stearic acid, and titanium dioxide. The 25 mg capsules also contain the following inactive ingredients: FD&C Blue No. 2 and strong ammonia solution. The 100 mg capsules also contain the following inactive ingredients: black iron oxide, FD&C Blue No. 1, FD&C Yellow No. 5, povidone, red iron oxide, and sodium hydroxide.

Manufactured for: Xcovery Holdings, Inc., Miami, FL, 33131

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For more information, call Xcovery Holdings, Inc. at (866) 367-2268.

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

Issued: 12/2024

NDC 83076-1025-3
Ensacove™
(ensartinib) capsules

25 mg

Rx Only

30 capsules

Each capsule contains ensartinib 25 mg (equivalent to 28.25 mg ensartinib hydrochloride).

Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store and dispense in the original bottle with desiccant to protect from moisture. Do not remove desiccant from bottle.

Keep out of reach of children.

Recommended Dosage:
See prescribing information.



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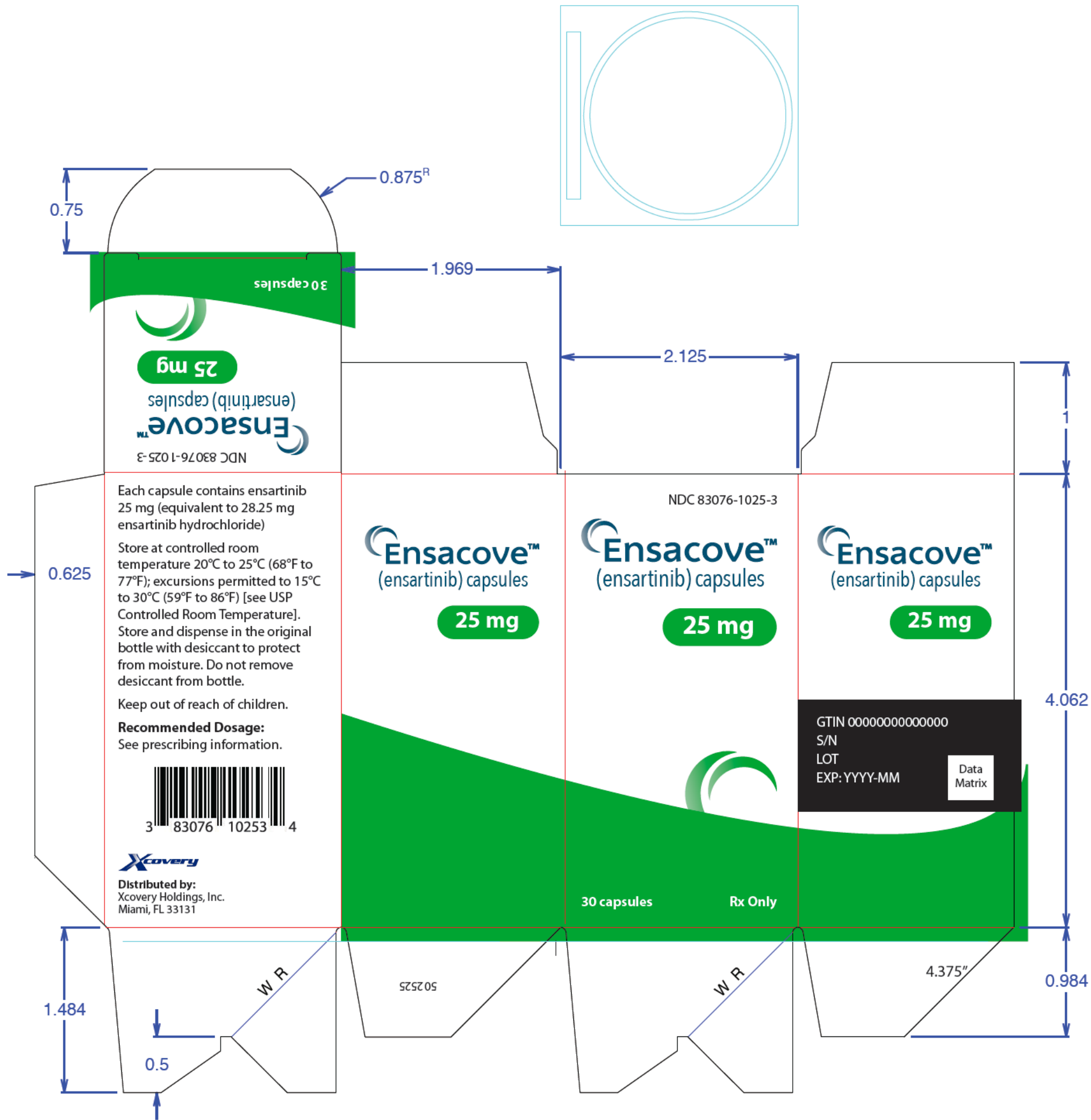
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Minimum font size: 5.5 pts



Minimum font size: 8.2 pts

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NDC 83076-1100-6
Ensacove™
(ensartinib) capsules

100 mg

Rx Only

60 capsules

Each capsule contains ensartinib 100 mg (equivalent to 113.02 mg ensartinib hydrochloride).

Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store and dispense in the original bottle with desiccant to protect from moisture. Do not remove desiccant from bottle.

Keep out of reach of children.

Recommended Dosage:
See prescribing information.



Distributed by:
Xcovery Holdings, Inc.
Miami, FL 33131

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1.55"

5.96"

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Minimum font size: 8.2 pts

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/s/

PAUL G KLUETZ
12/18/2024 02:50:22 PM