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

LYRFIGTU (lirafugratinib) capsules, for oral use
Initial U.S. Approval: 2026

----------INDICATIONS AND USAGE----------
LYRFIGTU is a kinase inhibitor indicated for the treatment of adults with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma harboring a FGFR2 fusion or other rearrangement. (1, 2.1)

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

Confirm the presence of an FGFR2 gene fusion or other rearrangement prior to initiation of treatment with LYRFIGTU. (2.1)

Recommended Dosage: 70 mg orally once daily with or without food. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 20 mg and 30 mg. (3)

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

----------WARNINGS AND PRECAUTIONS----------
- Ocular Toxicity: LYRFIGTU can cause retinal pigment epithelial detachment (RPED), blurred vision, dry eye, and corneal toxicity/keratitis. Perform a comprehensive ophthalmological examination, including OCT of the macula, prior to initiation of therapy, every 2 months for the first 13 months, and every 4 months thereafter and urgently at any time for visual symptoms. (2.3, 5.1)
- Hyperphosphatemia and Soft Tissue Mineralization: LYRFIGTU can cause hyperphosphatemia leading to soft tissue mineralization, calcinosis, nonuremic calciphylaxis, and vascular calcification. Monitor for hyperphosphatemia throughout treatment. (5.2)
- Embryo-Fetal Toxicity: LYRFIGTU can cause fetal harm. Advise patients of the potential risk to the fetus and to use effective contraception. (5.3, 8.1, 8.3)

----------ADVERSE REACTIONS----------
- Most common adverse reactions (≥20%) were nail toxicity, palmar-plantar erythrodysesthesia syndrome, stomatitis, alopecia, dry eye, dry mouth, fatigue, dysgeusia, retinal pigment epithelial detachment, constipation, dry skin, infection, rash, abdominal pain, hemorrhage, blurred vision, diarrhea, musculoskeletal pain, nausea, and decreased appetite. (6.1)
- Most common laboratory abnormalities (≥20%) were increased phosphate, increased alanine aminotransferase, increased creatinine, decreased hemoglobin, decreased sodium, decreased lymphocytes, increased blood bilirubin, increased aspartate aminotransferase, decreased platelets, increased glucose, decreased leukocytes, increased alkaline phosphatase, decreased albumin, decreased phosphate, decreased neutrophils, and decreased bicarbonate. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Elevar Therapeutics at 1-866-4ELEVAR or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong and Moderate CYP3A Inducers: Avoid concomitant use. (7.1)
- Strong and Moderate CYP3A Inhibitors: Avoid concomitant use. If concomitant use cannot be avoided, reduce LYRFIGTU dosage. (2.4, 7.1)

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Patient Information

Revised: 09/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LYRFIGTU is indicated for the treatment of adults with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma harboring a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of locally advanced or metastatic cholangiocarcinoma with LYRFIGTU based on the presence of an FGFR2 gene fusion or rearrangement *[see Clinical Studies (14)]*.

An FDA-authorized test for detection of FGFR2 gene fusions or other rearrangements in patients with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma for selecting patients for treatment with LYRFIGTU is not available.

2.2 Recommended Dosage

The recommended dosage of LYRFIGTU is 70 mg orally once daily until disease progression or unacceptable toxicity.

Take LYRFIGTU with or without food *[see Clinical Pharmacology (12.3)]*.

Swallow capsules whole. Do not open, break or chew the capsules.

If a dose of LYRFIGTU is missed, take the missed dose as soon as possible within 4 hours. If a dose is missed by 4 hours or more, skip the missed dose and take the dose at the next scheduled time.

If vomiting occurs after taking LYRFIGTU, do not take another dose. Take LYRFIGTU at the next scheduled time.

2.3 Dosage Modifications for Adverse Reactions

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

Table 1: Recommended Dosage Reductions for LYRFIGTU for Adverse Reactions

Dose Reduction	Dosage
First	50 mg once daily
Second	40 mg once daily
Third	30 mg once daily
Fourth	20 mg once daily

Permanently discontinue LYRFIGTU if the patient is unable to tolerate 20 mg once daily.

Recommended dosage modifications for adverse reactions are provided in Table 2.

Table 2: Recommended Dosage Modifications for LYRFIGTU Adverse Reactions

Adverse Reaction	Severity	LYRFIGTU Dosage Modification
Retinal Pigment Epithelial Detachment (RPED) *[see Warnings and Precautions (5.1)]*	Grade 1: Asymptomatic, no vision loss	Continue LYRFIGTU at the current dose and continue periodic ophthalmic evaluation
	Grade 2: Decrease in visual acuity to 20/40 to 20/200, or vision loss of 1-3 lines on a standard eye chart	Withhold LYRFIGTU until resolution, then resume at 1 dose level lower
	Grade 3: Decrease in visual acuity to 20/200 or worse, or vision loss of > 3 lines on a standard eye chart	Withhold LYRFIGTU until resolution, then resume at 2 dose levels lower
Other Adverse Reactions	Grade 3[a]	• Withhold LYRFIGTU until toxicity resolves to Grade ≤1 or baseline, then resume LYRFIGTU at 1 dose level lower. • If Grade 3 toxicity recurs, withhold LYRFIGTU until toxicity resolves to Grade ≤1 or baseline, then resume at 1 dose level lower or permanently discontinue LYRFIGTU.
	Grade 4[a]	• Withhold LYRFIGTU until toxicity resolves to Grade ≤2 or baseline, then resume LYRFIGTU at 1 dose level lower or permanently discontinue LYRFIGTU

[a] Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0).

2.4 Dosage Modification for CYP3A Inhibitors

The recommended dosage modifications for strong and moderate CYP3A inhibitors are provided in Table 3.

Table 3: Recommended Dosage Modification for Concomitant Use of Strong or Moderate CYP3A Inhibitors

Inhibitor	Dosage Modifications
Strong CYP3A	Avoid concomitant use. If concomitant use cannot be avoided, reduce LYRFIGTU dosage to 40 mg once daily.
Moderate CYP3A	Avoid concomitant use. If concomitant use cannot be avoided, reduce LYRFIGTU dosage to 50 mg once daily.

After a CYP3A inhibitor has been discontinued for 3 elimination half-lives, resume LYRFIGTU at the dosage that was used before starting the inhibitor *[see Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

LYRFIGTU Capsules:

20 mg: Opaque, white, size 3 capsules with “LIR” printed in black ink on the cap and “20 mg” printed in black ink on the body.

30 mg: Opaque, size 2 capsules with olive green cap and white body, with “LIR” printed in black ink on the cap and “30 mg” printed in black ink on the body.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Ocular Toxicity

Retinal Pigment Epithelial Detachment (RPED)

LYRFIGTU can cause RPED, which may cause symptoms such as blurred vision.

Among 385 patients who received LYRFIGTU *[see Adverse Reactions (6.1)]* and underwent ophthalmologic monitoring, including optical coherence tomography (OCT), RPED occurred in 31% of patients with 12% patients having Grade 2 and 1.8% Grade 3. The median time to onset of RPED was 57 days (range 4 to 221). RPED led to dose interruption of LYRFIGTU in 15% of patients, and dose reduction in 10% of patients.

Perform a comprehensive ophthalmological examination, including OCT of the macula, prior to initiation of therapy, every 2 months for the first 13 months, and every 4 months thereafter. For onset of visual symptoms, obtain ophthalmologic evaluation urgently, with follow-up every 3 weeks until resolution or discontinuation of LYRFIGTU.

Withhold or reduce the dose of LYRFIGTU as recommended *[see Dosage and Administration (2.3)]*.

Blurred Vision

Among 385 patients who received LYRFIGTU *[see Adverse Reactions (6.1)]*, blurred vision occurred in 18% of patients with Grade 3 events in 1.3% of patients.

Dry Eye

Among 385 patients who received LYRFIGTU *[see Adverse Reactions (6.1)]*, dry eye occurred in 38% of patients. Treat patients with ocular demulcents as needed.

Corneal Toxicity/Corneal Keratitis

Among 385 patients who received LYRFIGTU *[see Adverse Reactions (6.1)]*, corneal toxicity/keratitis occurred in 11% of patients. Treat patients with ocular demulcents as needed.

5.2 Hyperphosphatemia and Soft Tissue Mineralization

LYRFIGTU can cause hyperphosphatemia leading to soft tissue mineralization, calcinosis, nonuremic calciphylaxis, and vascular calcification.

Among 385 patients who received LYRFIGTU, hyperphosphatemia was reported in 21% of patients including Grade 2 events in 0.5% of patients *[see Adverse Reactions (6.1)]*. The median time to onset of hyperphosphatemia was 15 days (range 6-194). Hyperphosphatemia led to dose interruption in one (0.3%) patient and no permanent discontinuation. Phosphate binders were required in 7 (1.8%) patients who received LYRFIGTU.

Monitor patients for hyperphosphatemia throughout treatment.

5.3 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, LYRFIGTU can cause fetal harm or loss of pregnancy when administered to a pregnant woman. Oral administration of lirafugratinib to pregnant rats during the period of organogenesis caused embryo-fetal mortality, structural abnormalities, and fetal alterations to growth at maternal exposures below the human exposure at the 70 mg daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LYRFIGTU and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with LYRFIGTU and for 3 months 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:

- Ocular Toxicity *[see Warnings and Precautions (5.1)]*
- Hyperphosphatemia and Soft Tissue Mineralization *[see Warnings and Precautions (5.2)]*

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 safety population described in the WARNINGS AND PRECAUTIONS reflects exposure to LYRFIGTU 70 mg orally once daily in 385 patients with multiple advanced solid tumors evaluated in REFOCUS including 232 patients with cholangiocarcinoma and 153 patients with other advanced solid tumors. Among the 385 patients who received LYRFIGTU, 48% were exposed for 6 months or longer and 19% were exposed for greater than 12 months.

Previously Treated, Unresectable Locally Advanced or Metastatic Cholangiocarcinoma

The safety of LYRFIGTU was evaluated in REFOCUS, which included 116 patients with cholangiocarcinoma harboring FGFR2 gene fusions and other rearrangements who were previously treated with chemotherapy or chemoimmunotherapy, but naïve to FGFR inhibitor therapy *[see Clinical Studies (14)]*. Patients received LYRFIGTU 70 mg once daily until disease progression or unacceptable toxicity. Among the 116 patients who received LYRFIGTU, 73% were exposed for 6 months or longer and 37% were exposed for greater than 12 months.

Serious adverse reactions occurred in 32% of patients receiving LYRFIGTU. Serious adverse reactions in ≥2% of patients who received LYRFIGTU were infection (6%), pneumonia (3.4%), fatigue (2.6%), and hemorrhage (2.6%). A fatal adverse reaction of hemorrhage occurred in one patient.

Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received LYRFIGTU. Adverse reactions requiring permanent discontinuation of LYRFIGTU included palmar-plantar erythrodysesthesia syndrome (3 patients), stomatitis, anaphylactic reaction, and infection (1 patient each).

Dosage interruptions due to an adverse reaction occurred in 88% of patients who received LYRFIGTU 70 mg once daily. Adverse reactions requiring dose interruption in ≥5% of patients included palmar-plantar erythrodysesthesia syndrome, nail toxicity, stomatitis, retinal pigment

epithelial detachment, rash, infection, fatigue, blurred vision, corneal toxicity, blood bilirubin increased, alanine transferase increased, and pyrexia.

Dose reductions due to an adverse reaction occurred in 81% of patients who received LYRFIGTU. Adverse reactions requiring dose reductions in ≥2% of patients included palmar-plantar erythrodysesthesia syndrome, nail toxicity, stomatitis, retinal pigment epithelial detachment, rash, blurred vision, alanine aminotransferase increased, fatigue, aspartate aminotransferase increased, corneal toxicity and hyponatremia.

The most common adverse reactions (≥20%) were nail toxicity, palmar-plantar erythrodysesthesia syndrome, stomatitis, alopecia, dry eye, dry mouth, fatigue, dysgeusia, retinal pigment epithelial detachment, constipation, dry skin, infection, rash, abdominal pain, hemorrhage, blurred vision, diarrhea, musculoskeletal pain, nausea, and decreased appetite.

The most common laboratory abnormalities (≥20%) were increased phosphate, increased alanine aminotransferase, increased creatinine, decreased hemoglobin, decreased sodium, decreased lymphocytes, increased blood bilirubin, increased aspartate aminotransferase, decreased platelets, increased glucose, decreased leukocytes, increased alkaline phosphatase, decreased albumin, decreased phosphate, decreased neutrophils, decreased bicarbonate.

Table 4 summarizes the adverse reactions in REFOCUS. Table 5 summarizes laboratory abnormalities in REFOCUS.

Table 4: Adverse Reactions (>15%) in Patients Receiving LYRFIGTU in REFOCUS

Adverse Reaction [a]	LYRFIGTU N=116	
	All Grades[a] (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders		
Nail toxicity [b]	89	12
Palmar-plantar erythrodysaesthesia syndrome	82	33
Alopecia	66	0
Dry skin [b]	37	0
Rash [b]	34	5
Gastrointestinal disorders		
Stomatitis [b]	80	12
Dry mouth	50	0
Constipation	37	0.9
Abdominal pain [b]	28	3.4
Diarrhea	22	0.9
Nausea	21	1.7
Vomiting	16	0.9
Eye disorders [c]		
Dry eye [b]	53	0
Retinal pigment epithelial detachment [b]	38	1.7
Blurred vision [b]	22	0.9
Corneal toxicity [b]	16	0
Infections and infestations		
Infection [b]	34	8
Urinary tract infection [b]	19	0.9
General disorders and administration site conditions		

Fatigue [b]	43	3.4
Pyrexia	18	0.9
Edema [b]	17	0
Nervous system disorders		
Dysgeusia [b]	39	0.9
Neuropathy peripheral [b]	18	0.9
Vascular disorders		
Hemorrhage [b]	22	2.6
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain [b]	22	0
Metabolism and nutrition disorders		
Decreased appetite	20	0
Respiratory, thoracic and mediastinal disorders		
Nasal dryness	15	0

[a] Graded per NCI CTCAE 5.0
[b] includes multiple related terms
[c] evaluated by visual acuity testing, slit-lamp examination, fundoscopy with digital imaging, and optical coherence tomography (OCT) imaging occurred at Screening, every odd-numbered cycle from C3D1 to C13D1 and every other odd-numbered cycle thereafter (i.e., C17D1, C21D1, C25D1, etc.).

Table 5: Select Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients Receiving LYRFIGTU in REFOCUS

Laboratory Abnormality	**LYRFIGTU[a]**	
	All Grades[b] (%)	**Grade 3 or 4 (%)**
Chemistry		
Phosphate[c] increased	75	0
Alanine aminotransferase increased	53	7
Creatinine increased	52	0.9
Sodium decreased	49	20
Blood bilirubin increased	45	5
Aspartate aminotransferase increased	42	5
Glucose[d] increased	37	5
Alkaline phosphatase increased	26	1.7
Phosphate[d] decreased	25	5
Albumin decreased	25	0.9
Bicarbonate decreased	20	0
Potassium increased	19	2.6
Calcium corrected for albumin increased	17	2.6
Magnesium decreased	13	0
Potassium decreased	12	0
Hematology		
Hemoglobin decreased	49	8
Lymphocytes decreased	47	7
Platelets decreased	39	3.4
Leukocytes decreased	31	2.6
Neutrophils decreased	23	2.6

[a] The denominator used to calculate the rate varied from 65 to 116 based on the number of patients who had both baseline and at least one post-baseline laboratory measurement available.
[b] Graded per NCI CTCAE 5.0 lab toxicity criteria.
[c] NCI CTCAE 5.0 does not define grades for increased phosphate. Laboratory value shift table categories were used to assess increased phosphorus levels (Grades≥3 defined as >7mg/dL)
[d] Graded per NCI CTCAE 4.03.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on LYRFIGTU

Strong or Moderate CYP3A Inhibitors

Avoid concomitant use of LYRFIGTU with strong or moderate CYP3A inhibitors. Reduce LYRFIGTU dosage if concomitant use cannot be avoided *[see Dosage and Administration (2.4)]*.

Lirafugratinib is a substrate of CYP3A. Concomitant use of a strong or moderate CYP3A inhibitor increases lirafugratinib exposure *[see Clinical Pharmacology (12.3)]*, which may increase the risk of LYRFIGTU adverse reactions.

Strong or Moderate CYP3A Inducers

Avoid concomitant use of strong or moderate CYP3A inducers.

Concomitant use of LYRFIGTU with a strong or moderate CYP3A inducer may decrease lirafugratinib exposure *[see Clinical Pharmacology (12.3)]*, which may reduce the effectiveness of LYRFIGTU.

7.2 Effect of LYRFIGTU on Other Drugs

BCRP, P-gp, OATP1B1, and/or OATP1B3 Substrates

Monitor for increased adverse reactions for P-gp, BCRP, OATP1B1, and/or OATP1B3 substrates in which minimal concentration changes may lead to serious adverse reactions. Follow the recommended dosage modifications in the approved prescribing information for these substrates.

Lirafugratinib inhibits P-gp, BCRP, OATP1B1, and OATP1B3 in-vitro. Lirafugratinib may increase exposure of drugs that are substrates of P-gp, BCRP, OATP1B1, or OATP1B3, which may increase the risk of adverse reactions of these substrates *[see Clinical Pharmacology (12.3)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, LYRFIGTU can cause fetal harm or loss of pregnancy when administered to a pregnant woman. There are no available data on the use of LYRFIGTU in pregnant women. Oral administration of lirafugratinib to pregnant rats during the period of organogenesis resulted in embryo-fetal mortality, structural abnormalities, and fetal alterations to growth at maternal exposures below the human exposure at the 70 mg daily dose *[see Data]*. Advise pregnant women of the potential risk to a fetus.

In the US 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, administration of lirafugratinib to pregnant rats during the period of organogenesis resulted in 100% embryo-fetal mortality due to post-implantation loss at 125 mg/kg/day (approximately 0.4 times the human exposure based on AUC at the 70 mg daily dose). Decreased fetal body weight and increased limb malformations (ectrodactyly, absent or misshapen long bones), vascular and urogenital malformations, and skeletal variations occurred at 30 mg/kg/day (approximately 0.05 times the human exposure based on AUC at the 70 mg daily dose).

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with LYRFIGTU and for 6 months after the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with LYRFIGTU and for 3 months after the last dose.

Infertility

Males

Based on findings from animal studies, LYRFIGTU may impair male reproductive function and fertility. The effects on male reproductive organs in dogs were partially reversible [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and efficacy of LYRFIGTU have not been established in pediatric patients.

Animal Toxicity Data

In a repeat-dose toxicology study, administration of lirafugratinib to rats for 3 months resulted in marked odontoblast degeneration and fracture of the incisors at doses ≥ 50 mg/kg/day (approximately 0.1 times the human exposure based on AUC at the 70 mg daily dose).

8.5 Geriatric Use

Of the 385 patients treated with LYRFIGTU 70 mg once daily in REFOCUS, 32% were 65 years or older, and 7% of patients were 75 years or older. No clinically meaningful differences in safety or

effectiveness of LYRFIGTU have been observed between patients 65 years or older and younger adult patients.

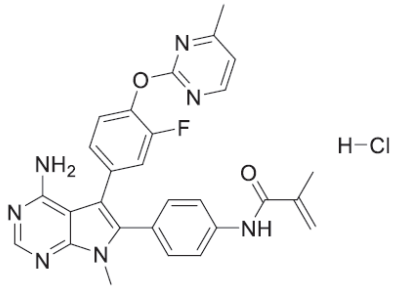
8.6 Hepatic Impairment

No dosage modifications are recommended for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. LYRFIGTU has not been studied in patients with severe (Child-Pugh Class C) hepatic impairment.

11 DESCRIPTION

Lirafugratinib hydrochloride is the salt form of lirafugratinib, a kinase inhibitor. It is white to off-white powder with the following chemical name: *N*-[4-[4-amino-5-[3-fluoro-4-(4-methylpyrimidin-2-yl) oxyphenyl]-7-methylpyrrolo[2,3-*d*]pyrimidin-6-yl]phenyl]-2-methylprop-2-enamide; hydrochloride. The active moiety is lirafugratinib.

Lirafugratinib hydrochloride is practically insoluble in water. The molecular formula for lirafugratinib hydrochloride is $C_{28}H_{25}ClFN_7O_2$ and the molecular weight is 546.0 g/mol. The chemical structure of lirafugratinib hydrochloride is:



Lirafugratinib capsules are supplied as printed hard gelatin capsules containing 20 mg and 30 mg of lirafugratinib. Each 20 mg LYRFIGTU capsule contains 21.43 mg of lirafugratinib hydrochloride (approximately 20 mg of lirafugratinib base), and each 30 mg LYRFIGTU capsule contains 32.15 mg of lirafugratinib hydrochloride (approximately 30 mg of lirafugratinib base).

Both capsule strengths contain the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and pregelatinized starch.

The capsule shell for both the 20 mg and 30 mg capsules includes gelatin, and titanium dioxide. The capsule shell for the 30 mg capsule also contains Black Iron Oxide (E172) and Yellow Iron Oxide (E172).

The black printing ink contains Black Iron Oxide (E172), butyl alcohol, dehydrated alcohol, isopropyl alcohol, propylene glycol, potassium hydroxide, purified water, shellac, and strong ammonia solution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lirafugratinib is a small molecule kinase inhibitor that inhibits FGFR2. Lirafugratinib covalently binds FGFR2. Constitutive FGFR signaling can support the proliferation and survival of malignant cells. Lirafugratinib inhibited FGFR2 phosphorylation and downstream signaling and decreased cell viability in cancer cell lines with FGFR2 alterations, including FGFR fusions/rearrangements, amplifications, and mutations. Lirafugratinib demonstrated anti-tumor activity in human cell line-derived and patient-derived xenograft mouse models of various tumors with FGFR2 genetic alterations.

12.2 Pharmacodynamics

Exposure-Response Relationships

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

Cardiac Electrophysiology

The largest mean increase in QTcF from baseline was 7 ms (upper confidence interval = 12 ms) after administration of LYRFIGTU 70 mg in patients with unresectable or metastatic cholangiocarcinoma or other advanced tumors.

12.3 Pharmacokinetics

Lirafugratinib pharmacokinetics were observed at steady- state in patients with cholangiocarcinoma or other solid tumors at the approved recommended dosage and are presented as mean (coefficient of variation [CV]%) unless otherwise specified. Lirafugratinib maximum concentration (C_{max}) is 4.7 mcg/mL (30%) and systemic exposure (AUC) is 77 mcg·h/mL (29%). Lirafugratinib AUC and C_{max} increases in a dose proportional manner over the dose range from 20 mg to 100 mg orally once daily (0.3 to 1.4 times the recommended dosage). Lirafugratinib accumulation is approximately 2-fold at the approved recommended dosage. Lirafugratinib steady state is reached in approximately 4 days.

Absorption

Lirafugratinib median (min, max) time to maximum plasma concentration (T_{max}) is 3.9 (1.9 to 8) hours.

Effect of Food

No clinically significant difference in lirafugratinib pharmacokinetics were observed following administration of a high-fat, high-calorie meal (approximately 800 to 1000 total calories with 500 to 600 calories from fat).

Distribution

Lirafugratinib apparent (oral) volume of distribution is 22 (22%) L. Lirafugratinib plasma protein binding is >99% and is not concentration-dependent in vitro. Lirafugratinib blood-to-plasma ratio is approximately 0.4.

Elimination

Lirafugratinib elimination half-life is 23 (34%) hours with an apparent (oral) clearance of 1 (32%) L/h.

Metabolism

Lirafugratinib is primarily metabolized by CYP3A4 and CYP2J2 and to a lesser extent by non-CYP enzymes in vitro.

Excretion

Following a single oral dose of radiolabeled lirafugratinib 70 mg to healthy subjects, approximately 80% of the dose was recovered in feces (23% unchanged), and 8% was recovered in urine (unchanged lirafugratinib not quantified).

Specific Populations

No clinically significant differences in the pharmacokinetics of lirafugratinib were observed based on age (20-87 years), sex, race (White 59%, Asian 16%, or Black 2.7%), body weight (34-147 kg), CLcr 30-89 mL/min (estimated by Cockcroft-Gault), or mild (Child-Pugh Class A) to moderate (Child-Pugh

Class B) hepatic impairment. The effect of severe renal impairment (CLcr < 30 mL/min) and severe (Child-Pugh Class C) hepatic impairment on lirafugratinib pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Strong and Moderate CYP3A Inhibitors: Lirafugratinib C_{max} increased 1.3-fold and AUC 2-fold following coadministration with itraconazole 200 mg once daily for 8 days.

Lirafugratinib C_{max} is predicted to increase 1.1-fold and AUC 1.7-fold following coadministration with erythromycin (moderate CYP3A inhibitor) 500 mg four times a day for 15 days.

Strong and Moderate CYP3A Inducers: Lirafugratinib C_{max} is predicted to decrease to 65% and AUC to 25% following coadministration of rifampicin (strong CYP3A inducer) 600 mg once daily for 19 days.

Lirafugratinib C_{max} is predicted to decrease to 85% and AUC to 43% following coadministration of efavirenz (moderate CYP3A inducer) 600 mg once daily for 19 days.

Other Drugs: No clinically significant differences in lirafugratinib pharmacokinetics are predicted when used concomitantly with quinidine (P-gp inhibitor). No clinically significant differences in lirafugratinib pharmacokinetics were observed when administered concomitantly with esomeprazole (proton pump inhibitor).

No clinically significant differences in the pharmacokinetics of the following drugs are predicted when used concomitantly with lirafugratinib: repaglinide (CYP2C8 substrate), tolbutamide (CYP2C9 substrate), omeprazole (CYP2C19 substrate), desipramine (CYP2D6 substrate), midazolam (CYP3A substrate), and caffeine (CYP1A2 substrate).

In Vitro Studies

CYP450 Enzymes: Lirafugratinib both induces and inhibits CYP2B6.

Transporter Systems: Lirafugratinib is a P-gp and BCRP substrate, but not of OCT1, OATP1B1, OATP1B3, or BSEP.

Lirafugratinib inhibits P-gp,MATE1, MATE2-K, OCT1, OCT2, OATP1B1, OATP1B3, BCRP, and BSEP, but does not inhibit OAT1 or OAT3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted with lirafugratinib.

Mutagenesis

Lirafugratinib was not mutagenic in the bacterial reverse mutation (Ames) assay. Lirafugratinib was clastogenic in the in vitro chromosomal aberration assay in human peripheral blood lymphocytes but not clastogenic in the in vivo peripheral blood reticulocyte micronucleus assay in rats.

Impairment of Fertility

Dedicated fertility studies with lirafugratinib have not been conducted. In repeat-dose toxicology studies, administration of lirafugratinib to male dogs for up to 3 months resulted in degeneration/atrophy in the seminiferous tubules and decreased epididymal sperm at doses ≥ 10

mg/kg/day (approximately 0.07 times the human exposure based on AUC at the 70 mg daily dose). Partial reversibility of these findings was observed following a recovery period.

13.2 Animal Toxicology and/or Pharmacology

Lirafugratinib absorbs UV radiation and demonstrated phototoxic potential in an in vitro phototoxicity study in BALB/c-3T3 mouse fibroblast cells. In rat tissue distribution studies, lirafugratinib was present in skin and pigmented eyes.

14 CLINICAL STUDIES

Cholangiocarcinoma

The efficacy of LYRFIGTU was evaluated in REFOCUS (RLY-4008-101; NCT04526106), a multicenter, open-label, single-arm trial in 116 patients with unresectable or metastatic cholangiocarcinoma who were naïve to FGFR inhibitor treatment and had received prior chemotherapy or chemoimmunotherapy. The presence of FGFR2 fusions or other rearrangements was determined in 112 (97%) enrolled patients using next-generation sequencing (NGS) testing. Qualifying in-frame fusions and other FGFR2 rearrangements were predicted to have a breakpoint within intron 17/exon 18 of the FGFR2 gene leaving the FGFR2 kinase domain intact.

Patients received LYRFIGTU 70 mg once daily until disease progression or unacceptable toxicity. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DoR) as determined by an independent review committee (IRC) according to RECIST v1.1.

The median age was 57 years (range 29- 81), 61% female, 55% White, 22% Asian, 1.7% Black or African American, 0.9% were other and 20% were unknown race or not reported; 5% Hispanic or Latino, 78% not Hispanic or Latino, and 16% were ethnicity unknown or not reported; 50% had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 50% had ECOG of 1, and 96% had intrahepatic cholangiocarcinoma. Ninety percent (90%) of patients had in-frame FGFR2 gene fusions; the most commonly identified FGFR2 fusion partner was BICC1 (n=30, 26%).

All patients had received at least one prior line of platinum-based systemic therapy, 28% had 2 prior lines of therapy, and 10% had 3 or more prior lines of therapy; 58% received prior gemcitabine/cisplatin without immunochemotherapy.

Efficacy results are summarized in Table 6. The median time to response was 1.9 months (range 1.1, 10.9 months).

Table 6: Efficacy Results in REFOCUS

Efficacy Parameter	**LYRFIGTU N = 116**
ORR (95% CI) [a]	46% (36, 55)
Complete response, n (%)	3 (2.6%)
Partial response, n (%)	50 (43%)
Median DoR (months) (95% CI)	11.8 (7.5, 13.0)
DoR ≥6 months, n (%)	33 (62)
DoR ≥12 months, n (%)	11 (21)

[a] The 95% confidence interval (CI) was calculated using the Clopper-Pearson method.

16 HOW SUPPLIED/STORAGE AND HANDLING

LYRFIGTU 20 mg capsules are opaque, white, size 3 capsules with “LIR” printed in black ink on the cap and “20 mg” printed in black ink on the body.

LYRFIGTU 30 mg capsules are opaque, size 2 capsules with olive green cap and white body, with “LIR” printed in black ink on the cap and “30 mg” printed in black ink on the body.

LYRFIGTU capsules are packaged in blister cards and supplied in child-resistant DosePaks™ as follows:

Daily Dose	Package Configuration	NDC
70 mg Daily Dose	Carton containing 84 capsules • 2 blister packs containing twenty-eight 20 mg capsules and fourteen 30 mg capsules each	82827-070-01
50 mg Daily Dose	Carton containing 56 capsules • 2 blister packs containing fourteen 20 mg capsules and fourteen 30 mg capsules each	82827-050-01
40 mg Daily Dose	Carton containing 56 capsules • 2 blister packs containing twenty-eight 20 mg capsules each	82827-040-01
30 mg Daily Dose	Carton containing 28 capsules • 1 blister pack containing twenty-eight 30 mg capsules	82827-030-01
20 mg Daily Dose	Carton containing 28 capsules • 1 blister pack containing twenty-eight 20 mg capsules	82827-020-01

Store at 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].

17 PATIENT COUNSELING INFORMATION

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

Ocular Toxicity

Advise patients that LYRFIGTU may cause ocular toxicity including RPED and that they will have their vision monitored during treatment. Advise patients to immediately inform their healthcare provider if they experience any visual changes *[see Warnings and Precautions (5.1)]*. Advise patients

to use artificial tears or hydrating or lubricating eye gels to prevent or treat dry eyes *[see Warnings and Precautions (5.1)]*.

Hyperphosphatemia and Soft Tissue Mineralization

Inform patients that LYRFIGTU may cause hyperphosphatemia and soft tissue mineralization and to immediately inform their healthcare provider of any symptoms related to acute change in phosphate levels such as muscle cramps, numbness, or tingling around the mouth *[see Warnings and Precautions (5.2)]*.

Nail Disorders

Advise patients that LYRFIGTU may cause nail disorders *[see Adverse Reactions (6.1)]*.

Embryo-Fetal Toxicity

- Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of pregnancy [*see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)]*.

- Advise females of reproductive potential to use effective contraception while on LYRFIGTU and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.
- Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of LYRFIGTU *[see Use in Specific Populations (8.3)]*.

Lactation

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

Phototoxicity

Inform patients that LYRFIGTU may cause phototoxicity and advise the use of sunscreen, protective clothing, and sunglasses, as well as minimizing sun exposure *[see Nonclinical Toxicology (13.2)]*.

Administration

Instruct patients to not open, break, or chew capsules.

Instruct patients if they miss a dose within 4 hours to take the missed dose. Instruct patients if they miss a dose by 4 or more hours or if they vomit after taking a dose not to take an additional dose and resume dosing with the next scheduled dose *[see Dosage and Administration (2.2)]*.

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, and herbal products.

Manufactured by
Quotient Sciences - Philadelphia, LLC
3 Chelsea Parkway
Boothwyn, PA 19061, USA

Packed by

Anderson Brecon (*dba PCI of Illinois*)
4545 Assembly Drive
Rockford, IL 61109, USA

Distributed by:
Elevar Therapeutics, Inc.
Fort Lee, NJ 07024, USA