HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LUCEMYRA™ (lofexidine) tablets, for oral use
Initial U.S. Approval: 2018

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

LUCEMYRA is a central alpha-2 adrenergic agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. (1)

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

- The usual LUCEMYRA dosage is three 0.18 mg tablets taken orally 4 times daily at 5- to 6-hour intervals. LUCEMYRA treatment may be continued for up to 14 days with dosing guided by symptoms. (2.1)
- Discontinue LUCEMYRA with a gradual dose reduction over 2 to 4 days. (2.1)
- Hepatic or Renal Impairment: Dosage adjustments are recommended based on degree of impairment. (2.2, 2.3)

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

Tablets: 0.18 mg. (3)

---------- CONTRAINDICATIONS ----------

None. (4)

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

- Risk of Hypotension, Bradycardia, and Syncope: May cause a decrease in blood pressure, a decrease in pulse, and syncope. Monitor vital signs before dosing and advise patients on how to minimize the risk of these cardiovascular effects and manage symptoms, should they occur. Monitor symptoms related to bradycardia and orthostasis. When using in outpatients, ensure that patients are capable of self-monitoring signs and symptoms. Avoid use in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or chronic renal failure, as well as in patients with marked bradycardia. (5.1)
- Risk of QT Prolongation: LUCEMYRA prolongs the QT interval. Avoid use in patients with congenital long QT syndrome. Monitor ECG in patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, hepatic or renal impairment, or in patients taking other medicinal products that lead to QT prolongation. (5.2)
- Increased Risk of CNS Depression with Concomitant use of CNS Depressant Drugs: LUCEMYRA potentiates the CNS depressant effects of benzodiazepines and may potentiate the CNS depressant effects of alcohol, barbiturates, and other sedating drugs. (5.3)
- Increased Risk of Opioid Overdose after Opioid Discontinuation: Patients who complete opioid discontinuation are at an increased risk of fatal overdose should they resume opioid use. Use in conjunction with a comprehensive management program for treatment of opioid use disorder and inform patients and caregivers of increased risk of overdose. (5.4)
- Risk of Discontinuation Symptoms: Instruct patients not to discontinue therapy without consulting their healthcare provider. When discontinuing therapy, reduce dose gradually. (5.5)

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

Most common adverse reactions (incidence ≥ 10% and notably more frequent than placebo) are orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact US WorldMeds at 1-833-LUCEMYRA or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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

- Methadone: Methadone and LUCEMYRA both prolong the QT interval. ECG monitoring is recommended when used concomitantly. (7.1)
- Oral Naltrexone: Concomitant use may reduce efficacy of oral naltrexone. (7.2)
- CYP2D6 Inhibitors: Concomitant use of paroxetine resulted in increased plasma levels of LUCEMYRA. Monitor for symptoms of orthostasis and bradycardia with concomitant use of a CYP2D6 inhibitor. (7.4)

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

Revised: 05/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUCEMYRA is indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults.

LUCEMYRA™ (lofexidine) tablets

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The usual LUCEMYRA starting dosage is three 0.18 mg tablets taken orally 4 times daily during the period of peak withdrawal symptoms (generally the first 5 to 7 days following last use of opioid) with dosing guided by symptoms and side effects. There should be 5 to 6 hours between each dose. The total daily dosage of LUCEMYRA should not exceed 2.88 mg (16 tablets) and no single dose should exceed 0.72 mg (4 tablets).

LUCEMYRA treatment may be continued for up to 14 days with dosing guided by symptoms.

Discontinue LUCEMYRA with a gradual dose reduction over a 2- to 4-day period to mitigate LUCEMYRA withdrawal symptoms (e.g., reducing by 1 tablet per dose every 1 to 2 days) *[see Warnings & Precautions (5.5)]*. The LUCEMYRA dose should be reduced, held, or discontinued for individuals who demonstrate a greater sensitivity to LUCEMYRA side effects *[see Adverse Reactions (6.1), Warnings and Precautions (5.1)]*. Lower doses may be appropriate as opioid withdrawal symptoms wane.

LUCEMYRA can be administered in the presence or absence of food.

2.2 Dosage Recommendations for Patients with Hepatic Impairment

Recommended dosage adjustments based on the degree of hepatic impairment are shown in Table 1. *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

Table 1: Dosage Recommendations in Patients with Hepatic Impairment

	Mild Impairment	Moderate Impairment	Severe Impairment
Child-Pugh score	5-6	7-9	> 9
Recommended dose	3 tablets 4 times daily (2.16 mg per day)	2 tablets 4 times daily (1.44 mg per day)	1 tablet 4 times daily (0.72 mg per day)

2.3 Dosage Recommendations for Patients with Renal Impairment

Recommended dosage adjustments based on the degree of renal impairment are shown in Table 2. LUCEMYRA may be administered without regard to the timing of dialysis *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

Table 2: Dosage Recommendations in Patients with Renal Impairment

	Moderate Impairment	Severe Impairment, End-Stage Renal Disease, or on Dialysis
Estimated GFR, mL/min/1.73 m^2	30-89.9	< 30
Recommended dose	2 tablets 4 times daily (1.44 mg per day)	1 tablet 4 times daily (0.72 mg per day)

3 DOSAGE FORMS AND STRENGTHS

LUCEMYRA is available as round, peach-colored, film-coated tablets, imprinted with “LFX” on one side and “18” on the other side. Each tablet contains 0.18 mg lofexidine (equivalent to 0.2 mg of lofexidine hydrochloride).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Hypotension, Bradycardia, and Syncope

LUCEMYRA can cause a decrease in blood pressure, a decrease in pulse, and syncope *[see Adverse Reactions (6.1), Clinical Pharmacology (12.2)]*. Monitor vital signs before dosing. Monitor symptoms related to bradycardia and orthostasis.

Patients being given LUCEMYRA in an outpatient setting should be capable of and instructed on self-monitoring for hypotension, orthostasis, bradycardia, and associated symptoms. If clinically significant or symptomatic hypotension and/or bradycardia occur, the next dose of LUCEMYRA should be reduced in amount, delayed, or skipped.

Inform patients that LUCEMYRA may cause hypotension and that patients moving from a supine to an upright position may be at increased risk for hypotension and orthostatic effects. Instruct patients to stay hydrated, on how to recognize symptoms of low blood pressure, and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position). Instruct outpatients to withhold LUCEMYRA doses when experiencing symptoms of hypotension or bradycardia and to contact their healthcare provider for guidance on how to adjust dosing.

Avoid using LUCEMYRA in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, chronic renal failure, and in patients with marked bradycardia.

Avoid using LUCEMYRA in combination with medications that decrease pulse or blood pressure to avoid the risk of excessive bradycardia and hypotension.

5.2 Risk of QT Prolongation

LUCEMYRA prolongs the QT interval.

Avoid using LUCEMYRA in patients with congenital long QT syndrome.

Monitor ECG in patients with congestive heart failure, bradyarrhythmias, hepatic impairment, renal impairment, or patients taking other medicinal products that lead to QT prolongation (e.g., methadone). In patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), correct these abnormalities first, and monitor ECG upon initiation of LUCEMYRA *[see Dosing and Administration (2.1), Adverse Reactions (6.1), Special Populations (8.6)(8.7), Clinical Pharmacology (12.2)]*.

5.3 Increased Risk of Central Nervous System Depression with Concomitant use of CNS Depressant Drugs

LUCEMYRA potentiates the CNS depressive effects of benzodiazepines and can also be expected to potentiate the CNS depressive effects of alcohol, barbiturates, and other sedating drugs. Advise patients to inform their healthcare provider of other medications they are taking, including alcohol.

Advise patients using LUCEMYRA in an outpatient setting that, until they learn how they respond to LUCEMYRA, they should be careful or avoid doing activities such as driving or operating heavy machinery.

5.4 Increased Risk of Opioid Overdose after Opioid Discontinuation

LUCEMYRA is not a treatment for opioid use disorder. Patients who complete opioid discontinuation are likely to have a reduced tolerance to opioids and are at increased risk of fatal overdose should they resume opioid use. Use LUCEMYRA in patients with opioid use disorder only in conjunction with a comprehensive management program for the treatment of opioid use disorder and inform patients and caregivers of this increased risk of overdose.

5.5 Risk of Discontinuation Symptoms

Stopping LUCEMYRA abruptly can cause a marked rise in blood pressure. Symptoms including diarrhea, insomnia, anxiety, chills, hyperhidrosis, and extremity pain have also been observed with LUCEMYRA discontinuation. Instruct patients not to discontinue therapy without consulting their healthcare provider. When discontinuing therapy with LUCEMYRA tablets, gradually reduce the dose *[see Dosing and Administration (2.1)]*.

Symptoms related to discontinuation can be managed by administration of the previous LUCEMYRA dose and subsequent taper.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Hypotension, Bradycardia, and Syncope *[see Warnings and Precautions (5.1)]*
- QT Prolongation *[see Warnings and Precautions (5.2)]*
- Central Nervous System Depression *[see Warnings and Precautions (5.3)]*
- Opioid Overdose *[see Warnings and Precautions (5.4)]*
- Discontinuation Symptoms *[see Warnings and Precautions (5.5)]*

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 adverse reaction rates observed for another drug and may not reflect the rates observed in practice.

The safety of LUCEMYRA was supported by three randomized, double-blind, placebo-controlled clinical trials, an open-label study, and clinical pharmacology studies with concomitant administration of either methadone, buprenorphine, or naltrexone.

The three randomized, double-blind, placebo-controlled clinical trials enrolled 935 subjects dependent on short-acting opioids undergoing abrupt opioid withdrawal. Patients were monitored before each dose in an inpatient setting.

Table 3 presents the incidence, rounded to the nearest percent, of adverse events that occurred in at least 10% of subjects treated with LUCEMYRA and for which the incidence in patients treated with LUCEMYRA was greater than the incidence in subjects treated with placebo in a study that tested two doses of LUCEMYRA, 2.16 mg per day and 2.88 mg per day, and placebo. The overall safety profile in the combined dataset was similar.

Orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth were notably more common in subjects treated with LUCEMYRA than subjects treated with placebo.

Table 3: Adverse Reactions Reported by ≥10% of LUCEMYRA-Treated Patients and More Frequently than Placebo

Adverse Reaction	LUCEMYRA 2.16 mg[1] (%) N=229	LUCEMYRA 2.88 mg[1] (%) N=222	Placebo (%) N=151
Insomnia	51	55	48
Orthostatic Hypotension	29	42	5
Bradycardia	24	32	5
Hypotension	30	30	1
Dizziness	19	23	3
Somnolence	11	13	5
Sedation	13	12	5
Dry Mouth	10	11	0

[1] Assigned dose; mean average daily dose received was 79% of assigned dose due to dose-holds for out-of-range vital signs.

Other notable adverse reactions associated with the use of LUCEMYRA but reported in <10% of patients in the LUCEMYRA group included:

- Syncope: 0.9%, 1.4% and 0% for LUCEMYRA 2.16 mg/day and 2.88 mg/day and placebo, respectively
- Tinnitus: 0.9%, 3.2% and 0% for LUCEMYRA 2.16 mg/day and 2.88 mg/day and placebo, respectively

Blood pressure changes and adverse reactions after LUCEMYRA cessation

Elevations in blood pressure above normal values (≥ 140 mmHg systolic) and above a subject's pre-treatment baseline are associated with discontinuing LUCEMYRA, and peaked on the second day after discontinuation, as shown in Table 4. Blood pressure values were evaluated for 3 days following the last dose of a 5-day course of LUCEMYRA 2.88 mg/day.

Table 4: Blood Pressure Elevations after Stopping Treatment

	Abrupt LUCEMYRA Discontinuation 2.88 mg (N = 134)		Placebo (N = 129)	
	N at risk	n (%)	N at risk	n (%)
Systolic Blood Pressure on Day 2 after Discontinuation				
≥ 140 mmHg and ≥ 20 mmHg increase from baseline	58	23 (39.7)	37	6 (16.2)
≥ 170 mmHg and ≥ 20 mmHg increase from baseline	58	5 (8.6)	37	0

Blood pressure elevations of a similar magnitude and incidence were observed in a small number of patients (N=10) that had a one-day, 50% dose reduction prior to discontinuation.

After stopping treatment, subjects that were taking LUCEMYRA also had a higher incidence of diarrhea, insomnia, anxiety, chills, hyperhidrosis, and extremity pain compared to subjects who were taking placebo.

Sex-specific adverse event findings

Four out of 101 females (4%) had serious cardiovascular adverse events compared to 3 out of 289 (1%) of males assigned to receive LUCEMYRA 2.88 mg per day.

Discontinuations and dose holds due to bradycardia and orthostatic hypotension, which are the most common adverse reactions associated with LUCEMYRA, occurred with a greater incidence in females assigned to receive the highest studied dose of LUCEMYRA, 2.88 mg per day as shown in Table 5.

Table 5: Discontinuations and Dose Holds for Bradycardia and Orthostatic Hypotension by LUCEMYRA Dose and Sex

	LUCEMYRA 2.16 mg	LUCEMYRA 2.88 mg
Male	22/162 (14%)	29/158 (18%)
Female	9/67 (13%)	20/64 (31%)

6.2 Postmarketing Experience

Lofexidine is marketed in other countries for relief of opioid withdrawal symptoms. The following events have been identified during postmarketing use of lofexidine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Since lofexidine's initial market introduction in 1992, the most frequently reported postmarketing adverse event with lofexidine has been hypotension *[see Warnings and Precautions (5.1)]*. There has been one report of QT prolongation, bradycardia, torsades de pointes, and cardiac arrest with successful resuscitation in a patient that received lofexidine and three reports of clinically significant QT prolongation in subjects concurrently receiving methadone with lofexidine.

7 DRUG INTERACTIONS

7.1 Methadone

LUCEMYRA and methadone both prolong the QT interval. ECG monitoring is recommended in patients receiving methadone and LUCEMYRA *[see Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.

7.2 Oral Naltrexone

Coadministration of LUCEMYRA and oral naltrexone resulted in statistically significant differences in the steady-state pharmacokinetics of naltrexone. It is possible that oral naltrexone efficacy may be reduced if used concomitantly within 2 hours of LUCEMYRA. This interaction is not expected if naltrexone is administered by non-oral routes *[see Clinical Pharmacology (12.3)]*.

7.3 CNS Depressant Drugs

LUCEMYRA potentiates the CNS depressant effects of benzodiazepines and may potentiate the CNS depressant effects of alcohol, barbiturates, and other sedating drugs. Advise patients to inform their healthcare provider of other medications they are taking, including alcohol *[see Warnings and Precautions (5.3)]*.

7.4 CYP2D6 Inhibitor - Paroxetine

Coadministration of LUCEMYRA and paroxetine resulted in 28% increase in the extent of absorption of LUCEMYRA. Monitor for orthostatic hypotension and bradycardia when an inhibitor of CYP2D6 is used concomitantly with LUCEMYRA *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety of LUCEMYRA in pregnant women has not been established. In animal reproduction studies, oral administration of lofexidine during organogenesis to pregnant rats and rabbits caused a reduction in fetal weights, increases in fetal resorptions, and litter loss at exposures below that in humans. When oral lofexidine was administered from the beginning of organogenesis through lactation, increased stillbirths and litter loss were noted along with decreased viability and lactation indices. The offspring exhibited delays in sexual maturation, auditory startle, and surface righting. These effects occurred at exposures below that in humans *[see Animal Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies carry some risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects in the U.S. general population is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

Increased incidence of resorptions, decreased number of implantations, and a concomitant reduction in the number of fetuses were observed when pregnant rabbits were orally administered lofexidine hydrochloride during organogenesis (from gestation day [GD] 7 to 19) at a daily dose of 5.0 mg/kg/day (approximately 0.08 times the maximum recommended human dose [MRHD] of 2.88 mg lofexidine base on an AUC basis). Maternal toxicity evidenced by increased mortality was noted at the highest tested dose of 15 mg/kg/day (approximately 0.4 times the MRHD on an AUC basis).

Decreased implantations per dam and decreased mean fetal weights were noted in a study in which pregnant rats were treated with oral lofexidine hydrochloride during organogenesis (from GD 7 to 16) at a daily dose of 3.0 mg/kg/day (approximately 0.9 times the MRHD on an AUC basis). This dose was associated with maternal toxicity (decreased body weight gain and mortality). No malformations or evidence of developmental toxicity were evident at 1.0 mg/kg/day (approximately 0.2 times the MRHD on an AUC basis).

A dose-dependent increase in pup mortality was noted in all doses of lofexidine hydrochloride administered orally to pregnant rats from GD 6 through lactation at an exposure less than the human exposure based on AUC comparisons. Doses higher than 1.0 mg/kg/day (approximately 0.2 times the MRHD on an AUC basis) resulted in incidences of total litter loss and maternal toxicity (piloerection and decreased body weight gain). The highest dose tested of 2.0 mg/kg/day (approximately 0.6 times the MRHD on an AUC basis), increased stillbirths as well as decreased viability and lactation indices were reported. Surviving offspring exhibited lower body weights, developmental delays, and increased delays in auditory startle at doses of 1.0 mg/kg/day or higher. Sexual maturation was delayed in male offspring (preputial separation) at 2.0 mg/kg/day and in female offspring (vaginal opening) at 1.0 mg/kg/day or higher.

8.2 Lactation

Risk Summary

There is no information regarding the presence of LUCEMYRA or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Caution should be exercised when LUCEMYRA is administered to a nursing woman.

The developmental and health benefits should be considered along with the mother's clinical need for LUCEMYRA and any other potential adverse effects on breastfed children from LUCEMYRA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

In animal studies that included some fertility endpoints, lofexidine decreased breeding rate and increased resorptions at exposures below human exposures. The impact of lofexidine on male fertility has not been adequately characterized in animal studies *[see Impairment of Fertility (13.1)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

No studies have been performed to characterize the pharmacokinetics of LUCEMYRA or establish its safety and effectiveness in geriatric patients. Caution should be exercised when it is administered to patients over 65 years of age. Dosing adjustments similar to those recommended in patients with renal impairment should be considered *[see Dosage and Administration (2.3), Use in Specific Populations (8.7)]*.

8.6 Hepatic Impairment

Hepatic impairment slows the elimination of LUCEMYRA but exhibits less effect on the peak plasma concentration than on AUC values following a single dose. Dosage adjustments are recommended based on the degree of hepatic impairment. *[see Dosage and Administration (2.2), Clinical Pharmacology (12.2)]*.

Clinically relevant QT prolongation may occur in subjects with hepatic impairment *[see Warnings and Precautions (5.2), Clinical Pharmacology (12.2)]*.

8.7 Renal Impairment

Renal impairment slows the elimination of LUCEMYRA but exhibits less effect on the peak plasma concentration than on AUC values following a single dose. Dosage adjustments are recommended based on the degree of renal impairment *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

Only a negligible fraction of the LUCEMYRA dose is removed during a typical dialysis session, so no additional dose needs to be administered after a dialysis session; LUCEMYRA may be administered without regard to the timing of dialysis *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

Clinically relevant QT prolongation may occur in subjects with renal impairment *[see Warnings and Precautions (5.2), Clinical Pharmacology (12.2)]*.

8.8 CYP2D6 Poor Metabolizers

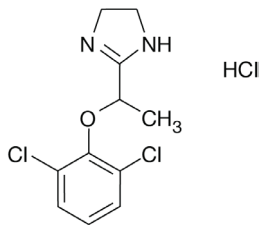
Although the pharmacokinetics of LUCEMYRA have not been systematically evaluated in patients who do not express the drug metabolizing enzyme CYP2D6, it is likely that the exposure to LUCEMYRA would be increased similarly to taking strong CYP2D6 inhibitors (approximately 28%). Monitor adverse events such as orthostatic hypotension and bradycardia in known CYP2D6 poor metabolizers. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Overdose with LUCEMYRA may manifest as hypotension, bradycardia, and sedation. In the event of acute overdose, perform gastric lavage where appropriate. Dialysis will not remove a substantial portion of the drug. Initiate general symptomatic and supportive measures in cases of overdosage.

11 DESCRIPTION

LUCEMYRA tablets contain lofexidine, a central alpha-2 adrenergic agonist, as the hydrochloride salt. Lofexidine hydrochloride is chemically designated as 2-[1-(2,6-dichlorophenoxy)ethyl]-4,5 dihydro-1*H*- imidazole monohydrochloride with a molecular formula of $C_{11}H_{12}Cl_2N_2O$•HCl. Its molecular weight is 295.6 g/mole and its structural formula is:



Lofexidine hydrochloride is a white to off-white crystalline powder freely soluble in water, methanol, and ethanol. It is slightly soluble in chloroform and practically insoluble in n-hexane and benzene.

LUCEMYRA is available as round, convex-shaped, peach-colored, film-coated tablets for oral administration. Each tablet contains 0.18 lofexidine, equivalent to 0.2 mg of lofexidine hydrochloride, and the following inactive ingredients: 92.6 mg lactose, 12.3 mg citric acid, 1.1 mg povidone, 5.7 mg microcrystalline cellulose, 1.4 mg calcium stearate, 0.7 mg sodium lauryl sulphate, and Opadry OY S 9480 (contains indigo carmine and sunset yellow).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lofexidine is a central alpha-2 adrenergic agonist that binds to receptors on adrenergic neurons. This reduces the release of norepinephrine and decreases sympathetic tone.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Single LUCEMYRA doses of 1.44 to 1.8 mg produced maximum mean change from baseline in QTcF (ΔQTcF) of 14.4 msec (upper two-sided 90% CI: 22.3 msec) and 13.6 msec (17.4 msec) for 1.44 and 1.8 mg respectively in healthy normal volunteers.

In a Phase 3 placebo-controlled, dose response study in opioid dependent subjects, LUCEMYRA was associated with a maximum mean prolongation of the QTcF interval 7.3 (8.8) and 9.3 (10.9) msec at doses of 2.16 and 2.88 mg/day, respectively.

Patients with hepatic impairment

Administration of LUCEMYRA to subjects with hepatic impairment was associated with prolongation of the QTc interval, which was more pronounced in subjects with severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

Patients with renal impairment

Administration of LUCEMYRA to subjects with renal impairment was associated with prolongation of the QTc interval, which was more pronounced in subjects with severe renal impairment *[see Use in Specific Populations (8.7)]*

LUCEMYRA coadministered with methadone

LUCEMYRA (2.88 mg/day) coadministered with methadone in 18 methadone-maintained patients (80-120 mg/day) resulted in a maximum mean increase from methadone-alone baseline in QTcF of 9.1 (14.2) msec.

LUCEMYRA coadministered with buprenorphine

LUCEMYRA (2.88 mg/day) coadministered with buprenorphine in 21 buprenorphine-maintained patients (16-24 mg/day) resulted in a maximum mean QTcF increase in QTcF of 15 (5.6) msec compared to a buprenorphine-alone baseline.

In Vitro Binding

LUCEMYRA exhibits *in vitro* binding affinity and functional agonist activity with alpha-2A and alpha-2C adrenoreceptors at concentrations within clinical exposure plasma levels (K_i values of approximately 7.2 nM and 12 nM, and EC_{50} values of 4.9 nM and 0.9 nM, respectively).

12.3 Pharmacokinetics

Absorption

LUCEMYRA is well absorbed and achieves peak plasma concentration 3 to 5 hours after administration of a single dose.

LUCEMYRA shows approximately dose-proportional pharmacokinetics. Administration of LUCEMYRA with food does not alter its pharmacokinetics.

The absolute bioavailability of a single oral LUCEMYRA dose (0.36 mg in solution) compared with an intravenous infusion (0.2 mg infused for 200 minutes) was 72%. Mean LUCEMYRA C_{max} after the oral dose and intravenous infusion was 0.82 ng/mL (at median T_{max} of 3 hours) and 0.64 ng/mL (at median T_{max} of 4 hours), respectively. Mean estimates of overall systemic exposure (AUC_{inf}) were 14.9 ng•h/mL and 12.0 ng•h/mL, respectively.

Distribution

Mean LUCEMYRA apparent volume of distribution and volume of distribution values following the administration of an oral dose and an intravenous dose were 480.0 L and 297.9 L, respectively, which are appreciably greater than total body volume, suggesting extensive LUCEMYRA distribution into body tissue.

LUCEMYRA protein binding is approximately 55%.

LUCEMYRA is not preferentially taken up by blood cells. In a study comparing LUCEMYRA concentrations in plasma and whole blood at the time of peak LUCEMYRA concentrations in human volunteers, it was determined that red blood cells contain approximately 27% the LUCEMYRA concentration of the plasma.

Elimination

Metabolism

From absolute bioavailability results, approximately 30% of the administered LUCEMYRA dose is converted to inactive metabolites during the first pass effect associated with drug absorption from the gut.

LUCEMYRA and its major metabolites did not induce or inhibit any CYP450 isoforms, with the exception of a slight inhibition of CYP2D6 by LUCEMYRA, with an IC_{50} of 4551 nM (approximately 225 times the steady-state C_{max} for LUCEMYRA with 0.72 mg 4 times daily dosing). Any LUCEMYRA interaction with CYP2D6 substrates is not expected to be clinically significant.

LUCEMYRA is metabolized when incubated *in vitro* with human liver microsomes, the major contributor to the hepatic metabolism of LUCEMYRA is CYP2D6, with CYP1A2 and CYP2C19 also capable of metabolizing LUCEMYRA.

Excretion

The elimination half-life is approximately 12 hours and mean clearance is 17.6 L/h following an IV infusion.

LUCEMYRA has a terminal half-life of approximately 11 to 13 hours following the first dose. At steady-state, the terminal half-life is approximately 17 to 22 hours. Accumulation occurs up to 4 days with repeat dosing, following the recommended dosing regimen.

A mass balance study of LUCEMYRA showed nearly complete recovery of radiolabel in urine (93.5%) over 144 hours postdose, with an additional 0.92% recovered in the feces over 216 hours postdose. Thus, it appears that all, or nearly all, of the dose was absorbed, and that the primary route of elimination of the parent drug and its metabolites is via the kidney. Renal elimination of unchanged drug accounts for approximately 15% to 20% of the administered dose.

Specific Populations

Hepatic Impairment

Hepatic impairment slows the elimination of LUCEMYRA, but exhibits less effect on the peak plasma concentration following a single dose. In a study comparing the pharmacokinetics of LUCEMYRA (0.36 mg) in mild, moderate, and severe hepatically impaired subjects to subjects with normal hepatic function (6 subjects in each hepatic function group), mean C_{max} values were similar for subjects with normal, mild, and moderate hepatic impairment as shown in Table 6.

Table 6: LUCEMYRA Pharmacokinetics in Subjects with Hepatic Impairment

	Normal	Mild Impairment	Moderate Impairment	Severe Impairment
Child-Pugh Class & Score	Normal Function	Class A 5-6	Class B 7-9	Class C 10-15
C_{max} % of normal	100	114	117	166
AUC_{last} % of normal	100	127	190	304
AUC_{∞} % of normal	100	117	185	260
$t_{1/2}$ % of normal	100	139	281	401

Renal Impairment

Renal impairment slows the elimination of LUCEMYRA but exhibits less effect on the peak plasma concentration following a single dose. In a study comparing the pharmacokinetics of LUCEMYRA (0.36 mg) in 8 end-stage renal disease subjects on 3 times weekly hemodialysis to 8 subjects with normal renal function matched for sex, age, and body mass index, mean C_{max} values were similar for end-stage renal disease and normal renal function subjects, indicating no change in maximum LUCEMYRA exposure with renal impairment as shown in Table 7.

The impact of dialysis on the overall pharmacokinetics of LUCEMYRA during a typical 4-hour dialysis was minimal; the drop in LUCEMYRA plasma concentrations produced during the dialysis session was transient, with a rebound to nearly predialysis concentrations after re-equilibration within a few hours following completion of the dialysis cycle *[see Dosage and Administration (2.3), Use in Specific Populations (8.7)]*.

In a study comparing the pharmacokinetics of LUCEMYRA (0.36 mg) in 6 subjects each with normal renal function, mild renal impairment, and moderate renal impairment as well as 5 subjects with severe renal impairment but not requiring dialysis, there were similar increases in mean C_{max} values in subjects with mild and moderate renal impairment in comparison to subjects with normal renal function with additional increase in mean C_{max} values in subjects with severe renal impairment. Mean AUC_{last}, AUC_{∞}, and $t_{1/2}$ increased with severity of renal impairment as shown in Table 7.

Table 7: LUCEMYRA Pharmacokinetics in Subjects with Renal Impairment

	Normal	Mild Impairment	Moderate Impairment	Severe Impairment	ESRD or on dialysis
eGFR (mL/min/1.73 m^2)	≥ 90	60-89	30-59	15-29	< 15
C_{max} % of normal	100	124	117	154	104
AUC_{last} % of normal	100	157	187	272	181
AUC_{∞} % of normal	100	144	173	243	171
$t_{1/2}$ % of normal	100	111	145	157	137

Drug Interaction Studies

LUCEMYRA coadministered with methadone

In a double-blind placebo-controlled study of 23 patients maintained on a methadone dose of 80-120 mg/day and concomitantly administered LUCEMYRA up to 2.88 mg/day, LUCEMYRA did not alter the pharmacokinetics of methadone. LUCEMYRA concentrations may be slightly increased when coadministered with methadone; however, the increase at concentrations expected with recommended dosing is not clinically meaningful *[see Drug Interactions (7.1)]*.

LUCEMYRA coadministered with buprenorphine

In a double-blind placebo-controlled study of 30 subjects maintained on buprenorphine (16-24 mg/day) concomitantly administered LUCEMYRA up to 2.88 mg/day, no pharmacokinetic or pharmacodynamic interactions between LUCEMYRA and buprenorphine were seen.

LUCEMYRA coadministered with oral naltrexone

In an open-label, single-arm study of 24 healthy subjects, oral naltrexone (50 mg/day) did not significantly alter the single-dose pharmacokinetics of LUCEMYRA (0.36 mg). The alteration in steady-state pharmacokinetics of oral naltrexone was statistically significant in the presence of LUCEMYRA. The t_{max} was delayed for both naltrexone and 6ß-naltrexol (2-3 hours), and overall exposure was slightly reduced when naltrexone was administered with LUCEMYRA *[see Drug Interactions (7.2)]*.

LUCEMYRA coadministered with paroxetine

In an open-label, single-sequence study of 24 healthy subjects, the strong CYP2D6 inhibitor paroxetine (40 mg/day) increased LUCEMYRA (0.36 mg) C_{max} and AUC_{∞} by approximately 11% and 28%, respectively *[see Drug Interactions (7.4)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No adequate long-term animal studies have been completed to evaluate the carcinogenic potential of lofexidine.

Mutagenesis

Lofexidine tested positive in the *in vitro* mouse lymphoma assay. Lofexidine tested negative in the *in vitro* bacterial reverse mutation assay (Ames assay) and in the *in vivo* rat micronucleus assay.

Impairment of Fertility

In a female fertility study in rabbits, fertility was not adversely impacted by administration of lofexidine hydrochloride up to 6.4 mg/kg/day (approximately 0.1 times the MRHD of 2.88 mg on an AUC basis) when administered orally to female rabbits starting 2 weeks prior to mating and through gestation and lactation. However, decreased breeding rate and higher post-implantation loss was observed at this dose, which correlated with higher resorptions and reduced litter size. Maternal toxicity, which included increased mortality rate, reduced body weight gain, and moderate sedation was observed at 6.4 mg/kg/day. The NOAEL for female fertility was 6.4 mg/kg/day and the NOAEL for female-mediated developmental parameters was 0.4 mg/kg/day (approximately 0.005 times the MRHD on an AUC basis).

In a fertility study in rats, fertility was unaffected by administration of lofexidine up to 0.88 mg/kg/day (approximately 0.2 times the MRHD on an AUC basis) via diet to male and female rats prior to mating and to the dams through gestation and lactation. No evidence of maternal toxicity was observed. However, no assessment of sperm or reproductive organs were performed in this study.

Reduced testes, epididymis, and seminiferous tubule weights, as well as delayed sexual maturation of males and females and decreases in the number of corpora lutea and implantations after mating, were noted in offspring of pregnant rats administered lofexidine hydrochloride orally from GD 6 through lactation at exposures less than the human exposure based on AUC comparisons.

14 CLINICAL STUDIES

Two randomized, double-blind, placebo-controlled trials supported the efficacy of LUCEMYRA.

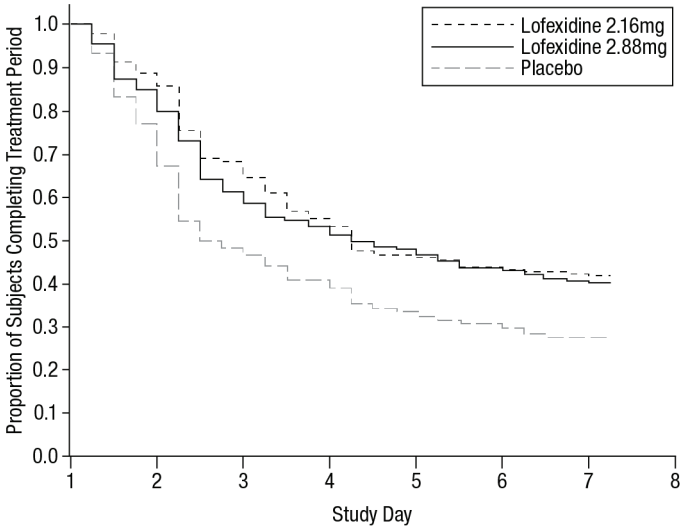
Study 1, NCT01863186

Study 1 was a 2-part efficacy, safety, and dose-response study conducted in the United States in patients meeting DSM-IV criteria for opioid dependence who were physically dependent on short-acting opioids (e.g., heroin, hydrocodone, oxycodone). The first part of the study was an inpatient, randomized, double-blind, placebo-controlled design consisting of 7 days of inpatient treatment (Days 1 – 7) with LUCEMYRA 2.16 mg total daily dose (0.54 mg 4 times daily) (n=229), LUCEMYRA 2.88 mg total daily dose (0.72 mg 4 times daily) (n=222), or matching placebo (n=151). Patients also had access to a variety of support medications for withdrawal symptoms (guaifenesin, antacids, dioctyl sodium sulfosuccinate, psyllium hydrocolloid suspension, bismuth sulfate, acetaminophen, and zolpidem). The second part of the study (Days 8 – 14) was an open-label design where all patients who successfully completed Days 1 – 7 were eligible to receive open-label treatment with variable dose LUCEMYRA treatment (as determined by the investigator, but not to exceed 2.88 mg total daily dose) for up to an additional 7 days (Days 8 – 14) in either an inpatient or outpatient setting as determined by the investigator and the patient. No patient received LUCEMYRA for more than 14 days.

The two endpoints to support efficacy were the mean Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop) total score on Days 1 – 7 of treatment and the proportion of patients that completed 7 days of treatment. The SOWS-Gossop, a patient-reported outcome (PRO) instrument, evaluates the following opioid withdrawal symptoms: feeling sick, stomach cramps, muscle spasms/twitching, feeling of coldness, heart pounding, muscular tension, aches and pains, yawning, runny eyes and insomnia/problems sleeping. For each opioid withdrawal symptom, patients are asked to rate their symptom severity using four response options (none, mild, moderate, and severe). The SOWS-Gossop total score ranges from 0 to 30 where a higher score indicates a greater withdrawal symptom severity. The SOWS-Gossop was administered at baseline and once daily 3.5 hours after the first morning dose on Days 1 – 7.

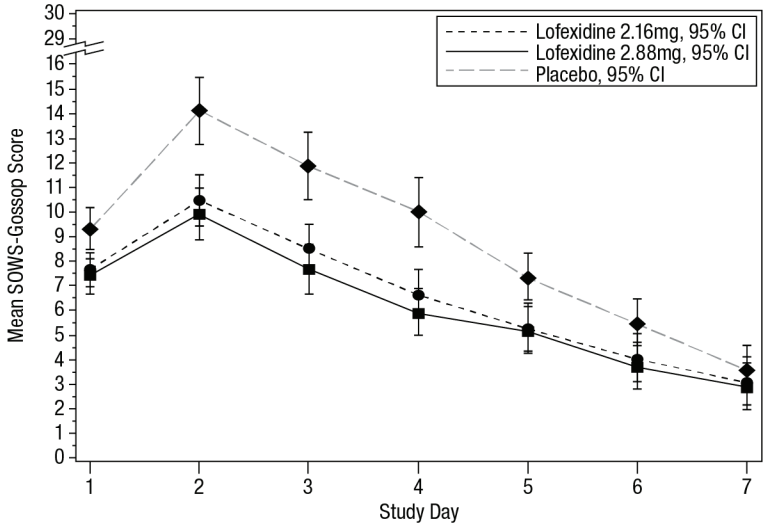
Of the randomized and treated patients, 28% of placebo patients, 41% of LUCEMYRA 2.16 mg and 40% of LUCEMYRA 2.88 mg patients completed 7 days of treatment. The difference in proportion in both LUCEMYRA groups was significant compared to placebo. See Figure 1. Patients in the placebo group were more likely to drop out of the study prematurely due to lack of efficacy than patients treated with LUCEMYRA.

Figure 1: Completion of treatment period for Study 1



The mean SOWS-Gossop scores for Days 1 – 7 were 8.8, 6.5, and 6.1 for placebo, LUCEMYRA 2.16 mg and LUCEMYRA 2.88 mg, respectively. Results are shown in Figure 2. The mean difference between LUCEMYRA 2.16 mg and placebo was -2.3 with a 95% CI of (-3.4, -1.2). The mean difference between LUCEMYRA 2.88 mg and placebo was -2.7 with a 95% CI of (-3.9, -1.6). They were both significant. Symptoms assessed on the SOWS-Gossop were recorded as absent or mild for almost all patients remaining to the end of the assessment period.

Figure 2: Mean SOWS-Gossop Scores for Days 1 – 7 in Study 1



Study 2, NCT00235729

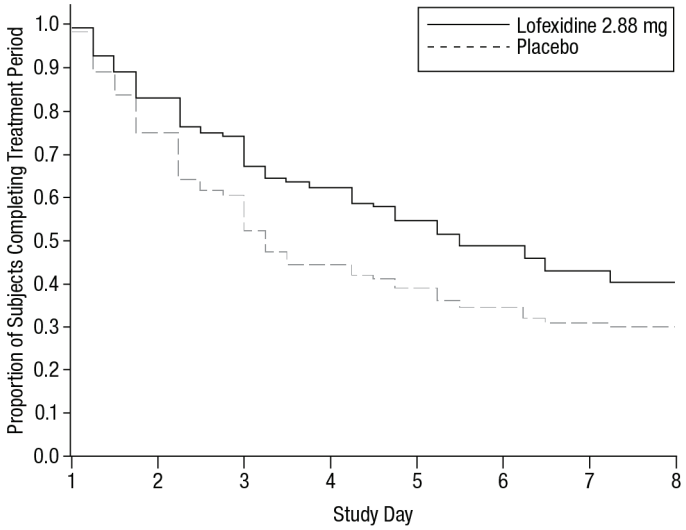
Study 2 was an inpatient, randomized, multicenter, double-blind, placebo-controlled study carried out in the United States in patients meeting DSM-IV criteria for opioid dependence who were physically dependent on short-acting opioids (e.g., heroin, hydrocodone, oxycodone). Patients were treated with LUCEMYRA tablets (2.88 mg/day [0.72 mg four times daily]) or matching placebo for 5 days (Days 1 – 5). Patients also had access to a variety of support medications for withdrawal symptoms (guaifenesin, antacids, dioctyl sodium sulfosuccinate, psyllium hydrocolloid suspension, bismuth sulfate, acetaminophen, and zolpidem). All patients then received placebo on Days 6 and 7 and were discharged on Day 8.

The two endpoints to support efficacy were the mean SOWS-Gossop total score on Days 1 – 5 of treatment and the proportion of patients that completed 5 days of treatment. The SOWS-Gossop was administered at baseline and once daily 3.5 hours after the first morning dose on Days 1 – 5.

A total of 264 patients were randomized into the study. Of these, 134 patients were randomized to LUCEMYRA 2.88 mg/day and 130 patients to placebo.

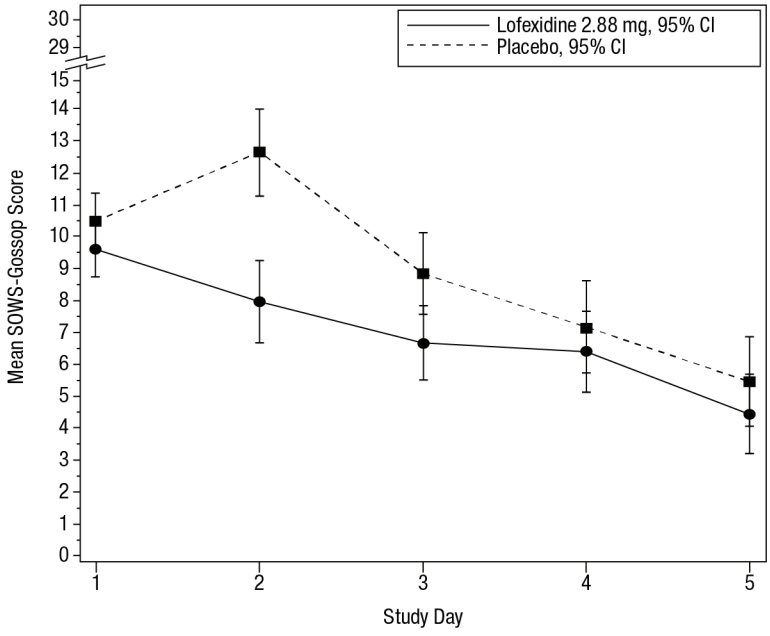
Of the randomized and treated patients, 33% of placebo patients and 49% of LUCEMYRA patients completed 5 days of treatment. The difference in proportion between the two groups was significant. See Figure 3. Patients in the placebo group were more likely to drop out of the study prematurely due to lack of efficacy than patients treated with LUCEMYRA.

Figure 3: Completion of treatment period in Study 2



The mean SOWS-Gossop scores for Days 1 – 5 were 8.9 and 7.0 for placebo and LUCEMYRA 2.88 mg, respectively. Results are shown in Figure 4. The mean difference was -1.9 with a 95% CI of (-3.2, -0.6) and was statistically significant.

Figure 4: Mean SOWS-Gossop Scores for Days 1 – 5 in Study 2



16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Available as 0.18 mg round, convex-shaped, peach colored, film-coated tablets, imprinted with “LFX” on one side and “18” on the other side; approximately 7 mm in diameter.

Bottles of 36 tablets . . . . . NDC 27505-050-36

Bottles of 96 tablets . . . . . NDC 27505-050-96

Storage

Store in original container at controlled room temperature, 25°C (77°F); with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Keep LUCEMYRA away from excess heat and moisture both in the pharmacy and after dispensing. Do not remove desiccant packs from bottles until all tablets are used. Keep LUCEMYRA and all medicines out of the reach of children.

17 PATIENT COUNSELING INFORMATION

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

LUCEMYRA may mitigate, but not completely prevent, the symptoms associated with opioid withdrawal syndrome, which may include feeling sick, stomach cramps, muscle spasms or twitching, feeling of cold, heart pounding, muscular tension, aches and pains, yawning, runny eyes and sleep problems (insomnia). Patients should be advised that withdrawal will not be easy. Additional supportive measures should be clearly advised, as needed.

Hypotension and Bradycardia

Inform patients to be alert for any symptoms of low blood pressure or pulse (e.g., dizziness, lightheadedness, or feelings of faintness at rest or on abruptly standing). Advise patients on how to reduce the risk of serious consequences should hypotension occur (sit or lie down, carefully rise from a sitting or lying position).

Patients being given LUCEMYRA in an outpatient setting should be capable of and instructed on self-monitoring for hypotension, orthostasis and bradycardia and advised to withhold LUCEMYRA doses and contact their healthcare provider for instructions if they experience these signs or related symptoms *[see Warnings and Precautions (5.1)]*.

Advise patients to avoid becoming dehydrated or overheated, which may potentially increase the risks of hypotension and syncope *[see Warnings and Precautions (5.1)]*.

Concomitant Medications

Review with patients all concomitant medications being taken and request that they immediately inform their healthcare provider of any changes in concomitant medications, including any other medications that may be used to treat individual symptoms of withdrawal.

Increased Risk of CNS Depression with Concomitant use of CNS Depressant Drugs

Inform patients of the increased risk of CNS depression with concomitant use of benzodiazepines, alcohol, barbiturates, or other sedating drugs *[see Warnings and Precautions (5.3)]*.

Advise patients using LUCEMYRA in an outpatient setting that, until they learn how they respond to LUCEMYRA, they should be careful or avoid doing activities such as driving or operating heavy machinery.

Sudden Discontinuation of LUCEMYRA

Inform patients not to discontinue LUCEMYRA without consulting their healthcare provider *[see Warnings and Precautions (5.5)]*.

Risk of Opioid Overdose After Discontinuation of Opioids

Advise patients that after a period of not using opioid drugs, they may be more sensitive to the effects of opioids and at greater risk of overdosing *[see Warnings and Precautions (5.4)]*.

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