



Elevate your standard
for opioid withdrawal care with LUCEMYRA.

Photos within this brochure are actor portrayals.

LUCEMYRA is the only FDA-approved, non-controlled treatment for relief of multiple symptoms of opioid withdrawal in adults.¹

Lucemyra[®]
(lofexidine) tablets 0.18 mg

Relieve the symptoms, retake control

Indication

LUCEMYRA is indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. **Please see the full Important Safety Information on page 11 and distributed full Prescribing Information and Patient Information.**

LUCEMYRA® treats the many symptoms of withdrawal ...

Treat imbalances caused by opioid use to reduce the severity of Opioid Withdrawal Syndrome (OWS)

Long-term opioid use changes the way nerve cells work in the brain²

- When opioids are initially taken, the brain produces lower levels of a naturally occurring hormone, called norepinephrine, that can affect breathing, muscle tension, and ability to sleep (Graphic 2)
- Continued use of opioids over time causes the nerve cells to increase their internal capabilities to restore normal levels of norepinephrine (Graphic 3)

When opioids are taken away suddenly, there is now an imbalance of too much norepinephrine²

- The person will begin to feel lots of very unpleasant feelings and reactions; these are known as withdrawal symptoms (Graphic 4)

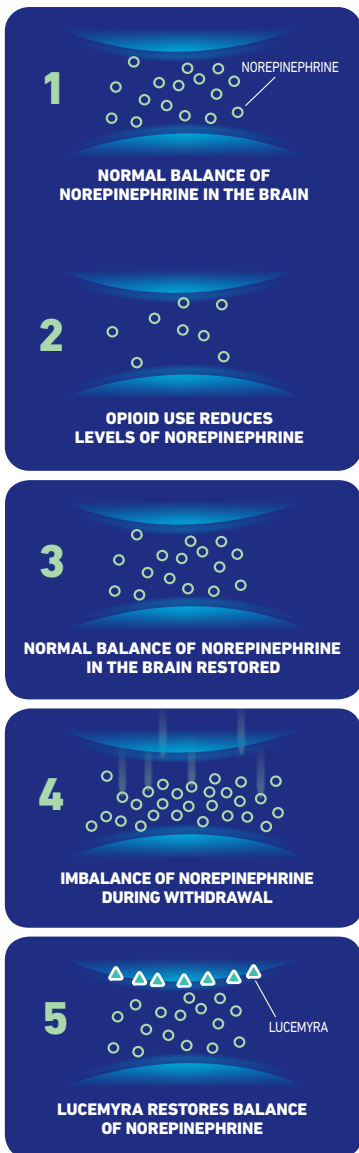
LUCEMYRA helps adjust the balance of norepinephrine in the areas of the brain that cause withdrawal symptoms¹

- This helps restore the chemical balance and helps relieve the symptoms that occur during opioid withdrawal (Graphic 5)

Avoidance of withdrawal is a driver of continued opioid use³



According to a survey of patients with OUD originally prescribed opioids for chronic pain, **more than half (57%)** reported that avoiding withdrawal symptoms was their primary reason for current use, rather than for pain relief (23%), or wanting to "get high" (14%).

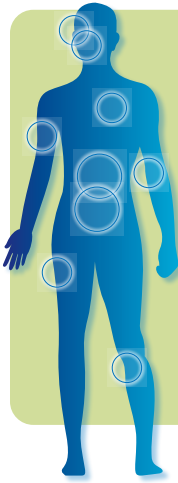


... and helps improve patient treatment success.

Opioid Withdrawal Syndrome (OWS) makes opioid discontinuation difficult and extremely unpleasant

Symptoms of opioid withdrawal, sometimes known as OWS, are associated with both psychological distress and physical discomfort²

- Signs and symptoms of OWS often present concurrently, ranging from actual physical pain, to emotional and sleep disturbances, to other bothersome sensations localizing in muscles, joints, skin, and other parts of the body²



Stopping opioid use suddenly can result in severe withdrawal symptoms, including^{4,5}:

- Runny eyes
- Yawning
- Heart pounding
- Stomach cramps
- Feelings of coldness (chills)
- Aches and pains
- Feeling sick (nausea, vomiting, diarrhea)
- Muscle spasms (twitching)
- Muscular tension
- Insomnia

Consider non-controlled treatment to help relieve withdrawal symptoms and facilitate abrupt opioid discontinuation

Important Safety Information

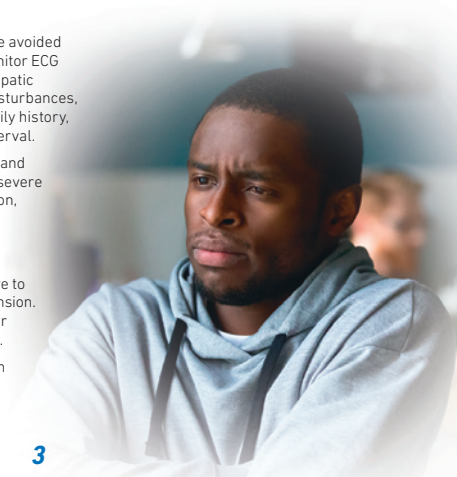
LUCEMYRA prolongs the QT interval and should be avoided in patients with congenital long QT syndrome. Monitor ECG in patients using LUCEMYRA who have renal or hepatic impairment, known QT prolongation, metabolic disturbances, pre-existing cardiovascular disease, relevant family history, or those taking drugs known to prolong the QT interval.

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

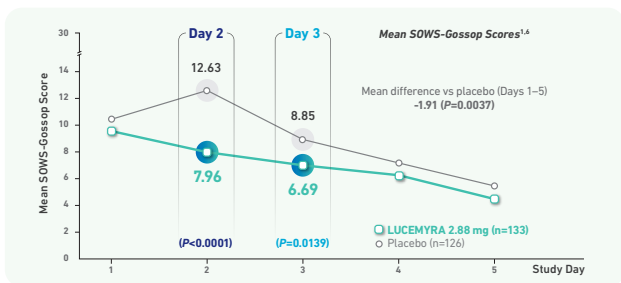
LUCEMYRA should be used with caution with any medications that decrease pulse or blood pressure to avoid the risk of excessive bradycardia and hypotension. Patients using LUCEMYRA should be monitored for symptoms related to bradycardia and orthostasis.

LUCEMYRA treatment should be discontinued with gradual dose reduction.

Please see the full Important Safety Information on page 11 and distributed full Prescribing Information and Patient Information.

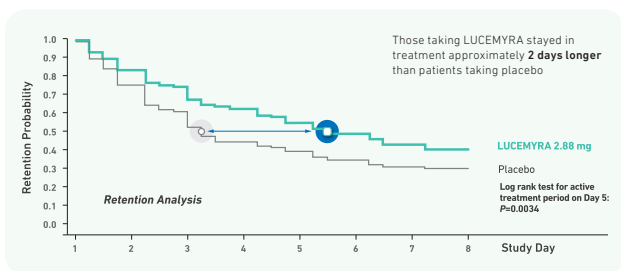


In a 5-day treatment study LUCEMYRA significantly reduced the severity of withdrawal symptoms^{1,6}



5-day study design^{1,4} US-based, phase 3, randomized, multicenter, double-blind, placebo-controlled study involving patients (N=264) who were dependent on opioids (based on DSM-IV™ criteria). The study utilized a parallel-group design that consisted of two main phases conducted over an 8-day period: a 5-day treatment phase and a 2-day post-treatment phase. During the 5-day treatment phase, one cohort received LUCEMYRA 2.88 mg total daily (0.72 mg four times daily), while the other cohort received a matching placebo dose four times daily. All patients received four placebo tablets QID on Days 6 and 7. On Day 8, patients did not receive medication and were discharged after completing the required assessments. Efficacy and safety were also assessed on Days 6-7. Clinical endpoints included mean SOWS-Gossop total score on Days 1 through 5 of treatment, and proportion of patients who completed 5 days of treatment.

Patients receiving LUCEMYRA were significantly more likely to stay in treatment, as compared with placebo (P=0.0034)^{1,6}



LUCEMYRA significantly improved the percentage of patients who successfully completed withdrawal treatment (P=0.0087)^{1,6}



Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop) is a subject-rated instrument that measures symptoms' severity⁵

- Reductions in SOWS-Gossop scores indicate alleviation of opioid withdrawal symptoms
- Score differences of approximately 2-4 points represent a clinically meaningful improvement on SOWS-Gossop assessments

Excerpts from a 2020 Focused Update of The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder

The updated Guideline from the American Society of Addiction Medicine (ASAM) discusses strategies for the treatment of opioid withdrawal, including updated treatment recommendations. This overview specifically focuses on the third section (**Part 3: Treating Opioid Withdrawal**) of the 2020 ASAM Guideline.

Recommendations for Treating Opioid Withdrawal¹

ASAM recognizes two main strategies for managing opioid withdrawal — gradually tapering the dose of opioid agonists, or employing the use of non-opioid alpha-2 adrenergic agonists.

Regarding the use of alpha-2 adrenergic agonists, the Guideline states:

“Lofexidine should therefore be the preferred choice for withdrawal management in an outpatient setting, where monitoring of blood pressure and management of hypotension is more difficult.”

— American Society of Addiction Medicine, 2020

Alpha-2 Adrenergic Agonists in Opioid Withdrawal Treatment

MAJOR
REVISION
IN 2020

Alpha-2 adrenergic agonists (such as FDA-approved lofexidine) are safe and effective non-opioid treatment options for managing withdrawal symptoms.¹ They can also be used concurrently with medications used to treat opioid use disorder.

The Guideline recommends that alpha-2 adrenergic agonists, such as LUCEMYRA® (lofexidine), can be used to treat withdrawal when patients:



Transition off
buprenorphine
or methadone



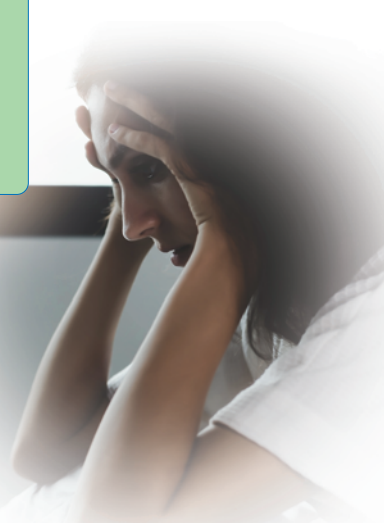
Prepare to start
extended-release
naltrexone

Important Safety Information

The most commonly reported adverse reactions associated with LUCEMYRA treatment (incidence $\geq 10\%$ and notably more frequent than placebo) are orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.

(ASAM). National practice guideline for the treatment of opioid use disorder: 2020 focused update. 2020. <https://www.asam.org/Quality-Science/quality/2020-national-practice-guideline>. Accessed July 13, 2020.

Please see the full Important Safety Information on page 11 and distributed full Prescribing Information and Patient Information.



LUCEMYRA is an in-patient or out-patient

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



For more information about treating the symptoms of opioid

nt treatment for patients experiencing:



Opioid Detox

Help patients mitigate withdrawal symptoms when seeking an opioid-free in-patient or out-patient treatment program.

Initiation of Buprenorphine

Prior to the induction of sublingual buprenorphine, ease patient through the period of abstinence required to avoid precipitating withdrawal.

Transition from Methadone to Buprenorphine

Help alleviate withdrawal symptoms in patients discontinuing methadone prior to a buprenorphine regimen.

Transition to Extended-Release Naltrexone

Help mitigate withdrawal symptoms during the 7- to 14-day abstinence period for patients transitioning to extended-release naltrexone injections.

Unplanned Disruptions in Treatment

Help mitigate withdrawal symptoms in patients with unplanned disruption of opioid treatment when opioid-agonists are unavailable or inappropriate for the situation.

After-Treatment Care

Help patients who have completed a successful MAT regimen with buprenorphine or methadone and are set to experience withdrawal symptoms from final step-down off treatment.

Important Safety Information

During and after opioid discontinuation, patients are at an increased risk of fatal overdose should they resume opioid use; patients and caregivers should be informed of this increased risk. In patients with opioid use disorder, LUCEMYRA should be used in conjunction with a comprehensive treatment program.

Dosing guided by symptoms¹

LUCEMYRA should be taken orally, four times per day, for the expected duration of withdrawal symptoms

Usual LUCEMYRA starting dosage:

Three 0.18 mg tablets (0.54 mg) taken orally 4 times daily during peak withdrawal symptoms (generally, this is the first 5 to 7 days after the last use of an opioid). A lower starting dose can be considered.

Dosing for LUCEMYRA should be guided by symptoms and side effects

A lower dose can be considered for patients with less severe symptoms or patients who present with additional concerns such as advanced age, low weight, or poor tolerability.



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 can be taken with or without food



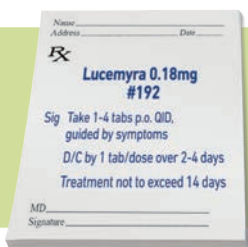
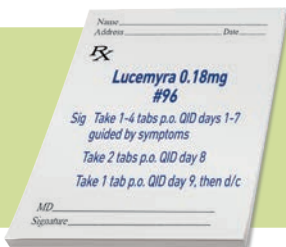
LUCEMYRA treatment may be continued for up to 14 days as guided by symptoms

In the prescription, include instructions for discontinuing LUCEMYRA



Discontinue LUCEMYRA with **Gradual dose reduction** over a 2- to 4-day period (e.g., reducing by 1 tablet per dose every 1 to 2 days)

Examples of dosing guided by symptoms¹



LUCEMYRA was studied in phase I drug interaction studies with commonly used therapies for Opioid Use Disorder: buprenorphine, methadone, and oral naltrexone

- LUCEMYRA and methadone both prolong the QT interval. ECG monitoring is recommended in patients receiving methadone and LUCEMYRA
- 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

LUCEMYRA safety profile¹

Adverse reactions reported by ≥10% of LUCEMYRA-treated patients and more frequently than placebo

Adverse Reaction	LUCEMYRA 2.16 mg* (N=229)	Placebo (N=151)
Insomnia	51%	48%
Orthostatic Hypotension	29%	5%
Bradycardia	24%	5%
Hypotension	30%	1%
Dizziness	19%	3%
Somnolence	11%	5%
Sedation	13%	5%
Dry Mouth	10%	0%

Adverse reactions* reported by ≥10% of patients receiving LUCEMYRA 2.88 mg** (N=222) included insomnia (55%), orthostatic hypotension (42%), bradycardia (32%), hypotension (30%), dizziness (23%), somnolence (13%), sedation (12%), and dry mouth (11%)

*U.S.-based, phase 3, randomized, multicenter, double-blind, placebo-controlled, two-part study examining the efficacy, safety, and dose-response in patients (N=602) dependent on opioids (based DSM-IV™ criteria). The first part of the study included 3 cohorts treated over 7 days following abrupt opioid discontinuation.¹

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

LUCEMYRA may lead to hypotension, bradycardia, or syncope

- If clinically significant or symptomatic hypotension and/or bradycardia occur, the next dose of LUCEMYRA should be reduced in amount, delayed, or skipped
- Syncope occurred in less than 3% of patients receiving LUCEMYRA compared to 0% of patients receiving placebo

Avoid using LUCEMYRA in certain patient populations, including:

- Patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or chronic renal failure, and in patients with marked bradycardia
- Patients taking any medications that decrease pulse or blood pressure to avoid the risk of excessive bradycardia and hypotension

There are no contraindications associated with LUCEMYRA



US WorldMeds is committed to helping patients

LUCEMYRA Prescription Savings Program

Eligible patients will pay as little as \$0* for LUCEMYRA

Lucemyra
(lofexidine) tablets 0.18 mg

Prescription Savings Program

Eligible patients will pay as little as \$0* for LUCEMYRA

Note: Discounts will be automatically applied; physical card not necessary.

See full offer details at LUCEMYRA.com
*Not valid for prescriptions paid for by government-funded health insurance.

Powered By:
RelayHealth | CHANGE
HEALTHCARE

Nearly all pharmacies in the U.S. are covered through the Relay Health, eRx Network, and McKesson programs[†]

*Patients whose prescriptions will be paid for in part or in whole by Medicare, Medicaid, or any similar federal or state healthcare program, are not eligible for savings or rebates according to federal and state law. Patients must visit a participating pharmacy for savings or rebates on their LUCEMYRA prescriptions. Maximum benefits may apply. Other restrictions may apply. For more information, please see Terms and Conditions at LUCEMYRA.com.

[†]Relay Health eVoucherRx Program and eRx Network are both paperless, and the discount is automatically applied at the pharmacy counter. McKesson is the only program that requires patients to provide the pharmacy with the ID number from their savings card to obtain the discount.

Tell your patients they can download their savings card from the Support & Savings page of LUCEMYRA.com

US WorldMeds Patient Assistance Program

- US WorldMeds recognizes that some people may not have health insurance and may not be able to pay for LUCEMYRA on their own
- US WorldMeds Patient Assistance Program (UPAP) provides LUCEMYRA to those patients who meet certain income requirements at no cost to the patient
- Please visit LUCEMYRA.com for more information, including how to get a UPAP Application and apply for the program

Important Safety Information

Dose adjustment of LUCEMYRA is required in patients with hepatic or renal impairment. Before prescribing, see dosage recommendation tables in Full Prescribing Information.

LUCEMYRA potentiates the depressant effects of benzodiazepines and may potentiate the CNS depressant effects of alcohol, barbiturates, and other sedating drugs.

References: 1. LUCEMYRA® (lofexidine) [Prescribing Information]. USWM, LLC; 2020. 2. Kosten TR, George TP. The neurobiology of opioid dependence: implications for treatment. *Sci Pract Perspect.* 2002;13-20. 3. Weiss RD, Potter JS, Griffith ML, et al. Reasons for opioid use among patients with dependence on prescription opioids: the role of chronic pain. *J Subst Abuse Treat.* 2014;47(2):140-145. 4. Shigakova F. Clinical manifestations of the opiate withdrawal syndrome. *Int J Biomed.* 2015;5(3):151-154. 5. Vernon MK, Reinders S, Mannix S, et al. Psychometric evaluation of the 10-item Short Opiate Withdrawal Scale-Gossop (SOWS-Gossop) in patients undergoing opioid detoxification. *Addict Behav.* 2016;60:109-116. 6. Data on file. US WorldMeds; 2017. 7. (ASAM). National practice guideline for the treatment of opioid use disorder: 2020 focused update. 2020. <https://www.asam.org/Quality-Science/quality/2020-national-practice-guideline>. Accessed July 13, 2020.

Important Safety Information

Indication

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

Important Safety Information

LUCEMYRA may cause hypotension, bradycardia, and syncope. Avoid using LUCEMYRA in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, chronic renal failure, or marked bradycardia. LUCEMYRA should be used with caution with any medications that decrease pulse or blood pressure to avoid the risk of excessive bradycardia and hypotension. Patients using LUCEMYRA should be monitored for symptoms related to bradycardia and orthostasis.

LUCEMYRA prolongs the QT interval and should be avoided in patients with congenital long QT syndrome. Monitor ECG in patients using LUCEMYRA who have renal or hepatic impairment, known QT prolongation, metabolic disturbances, pre-existing cardiovascular disease, relevant family history, or those taking drugs known to prolong the QT interval.

LUCEMYRA potentiates the depressant effects of benzodiazepines and may potentiate the CNS depressant effects of alcohol, barbiturates, and other sedating drugs.

During and after opioid discontinuation, patients are at an increased risk of fatal overdose should they resume opioid use; patients and caregivers should be informed of this increased risk. In patients with opioid use disorder, LUCEMYRA should be used in conjunction with a comprehensive treatment program.

LUCEMYRA treatment should be discontinued with gradual dose reduction.

The most commonly reported adverse reactions associated with LUCEMYRA treatment (incidence $\geq 10\%$ and notably more frequent than placebo) are orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.

Dose adjustment of LUCEMYRA is required in patients with hepatic or renal impairment. Before prescribing, see dosage recommendation tables in Full Prescribing Information.

There are no contraindications for taking LUCEMYRA.

To report SUSPECTED ADVERSE REACTIONS or product complaints, contact US WorldMeds at 1-833-LUCEMYRA.

You may also report SUSPECTED ADVERSE REACTIONS to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.



Plan for opioid discontinuation with the only FDA-approved, non-controlled treatment for relief of multiple symptoms of opioid withdrawal in adults.¹

Lucemyra
(lofexidine) tablets 0.18 mg

Relieve the symptoms, retake control



Improves success rates for completing treatment

LUCEMYRA significantly improved the percentage of patients who successfully completed withdrawal treatment^{1,6} ($P \leq 0.01$)^{1,6}



Demonstrated safety profile

The safety of LUCEMYRA is supported across three randomized, double-blind, placebo-controlled clinical trials¹



Significantly reduces symptom severity

LUCEMYRA demonstrated significant improvement when symptoms were most severe ($P \leq 0.01$)^{1,6}



Prescription savings discount

Eligible patients will pay as little as \$0* for their LUCEMYRA prescription. *See page 8 for program Terms and Conditions.



Learn more at
[LUCEMYRA.com](https://www.lucemyra.com)

Indication

LUCEMYRA is indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults.⁶

Please see the full Important Safety Information on page 11 and distributed full Prescribing Information and Patient Information.

US Worldmeds®

USWM, LLC, 4441 Springdale Road
Louisville, KY 40241

Under license from Britannia Pharmaceuticals Ltd.
USWM, LLC is the exclusive licensee and distributor of
LUCEMYRA in the United States and its territories.

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USWMLUC-00504 02/23

LUCEMYRA- lofexidine hydrochloride tablet, film coated

USWM, LLC

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 for 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 \geq 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: 9/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

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 *Warnings and Precautions (5.1), Adverse Reactions (6.1)*]. 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 on 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, 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 $\geq 10\%$ of LUCEMYRA-Treated Patients and More Frequently than Placebo

Adverse Reaction	LUCEMYRA 2.16 mg* (%) N=229	LUCEMYRA 2.88 mg* (%) 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

* 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 who 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%) males assigned to receive LUCEMYRA 2.88 mg/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/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%)
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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 who 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 concomitantly [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 a 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). At 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 to establish its safety and effectiveness in geriatric patients. Caution should be exercised when LUCEMYRA 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 (12.3)*].

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

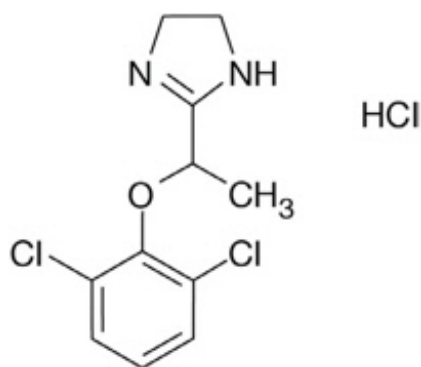
exposure to LUCEMYRA would be increased similarly to taking strong CYP2D6 inhibitors (approximately 28%). Monitor adverse events such as orthostatic hypotension and bradycardia in known CYP2D6 poor metabolizers. Approximately 8% of Caucasians and 3 to 8% of Black/African Americans cannot metabolize CYP2D6 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 $C_{11}H_{12}Cl_2N_2O \cdot HCl$. 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 mg to 1.8 mg produced maximum mean change from baseline in QTcF (Δ QTcF) of 14.4 msec (upper two-sided 90% CI: 22.3 msec) and 13.6 msec (17.4 msec) for 1.44 mg 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) msec and 9.3 (10.9) msec at doses of 2.16 mg/day 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 to 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 to 24 mg/day) resulted in a maximum mean QTcF increase of 1.5 (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 EC₅₀ 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 increases 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)	> 90	60-90	30-60	15-30	< 15

m ²)	≤ 30	30-60	30-50	10-20	> 10
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 methadone (80 to 120 mg/day) 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 to 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 6β-naltrexol (2 to 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 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

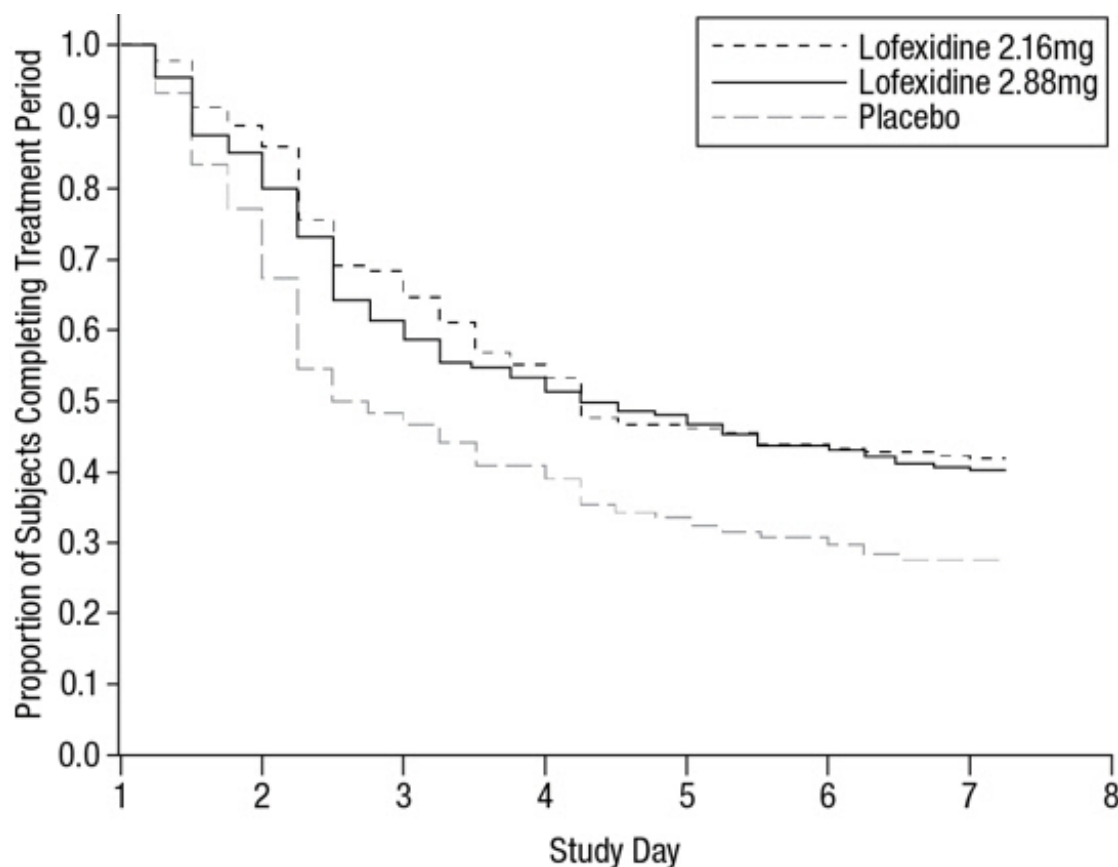
Study 1 was a 2-part efficacy, safety, and dose-response study conducted in the United States in patients meeting DSM-IV criteria for opioid dependence who were physically dependent on short-acting opioids (e.g., heroin, hydrocodone, oxycodone). The first part of the study was an inpatient, randomized, 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 who 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 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.

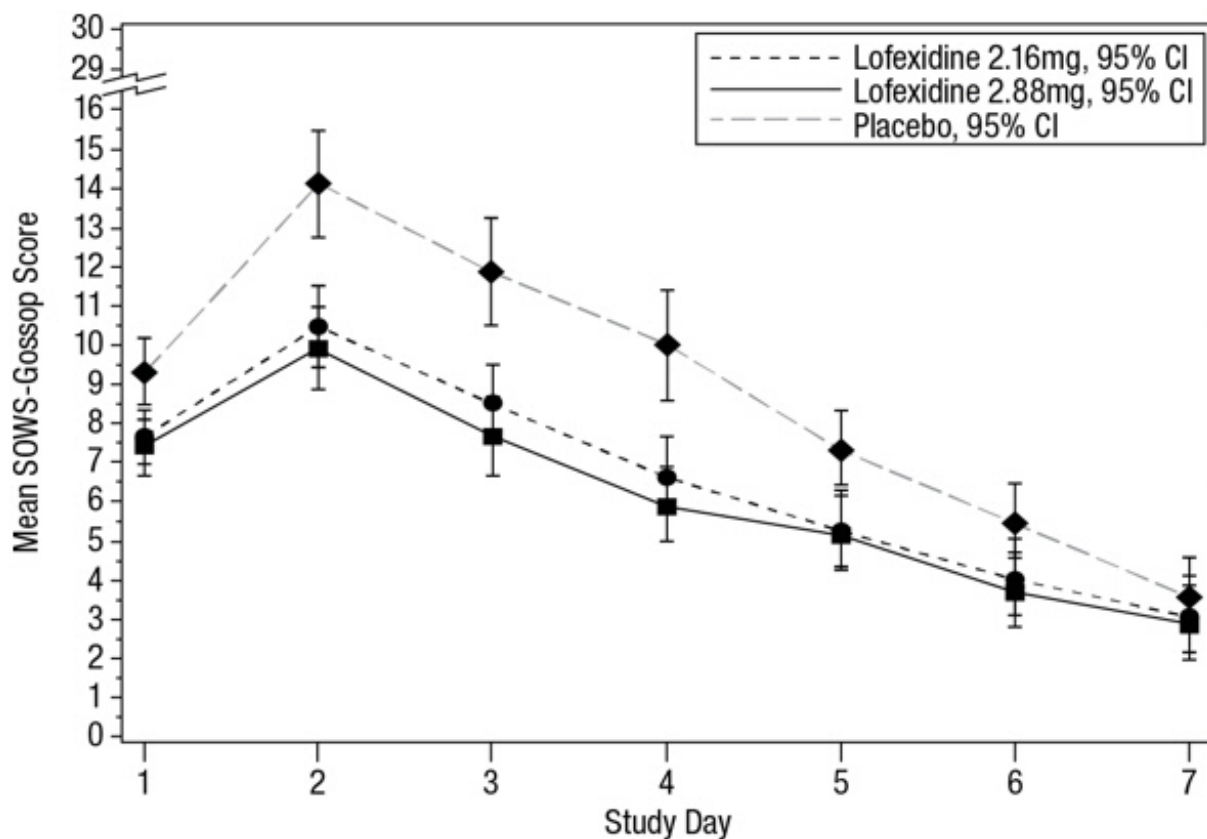
Of the randomized and treated patients, 28% of placebo patients, 41% of LUCEMYRA 2.16 mg and 40% of LUCEMYRA 2.88 mg patients completed 7 days of treatment. The difference in proportion in both LUCEMYRA groups was significant compared to placebo. See Figure 1. Patients in the placebo group were more 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

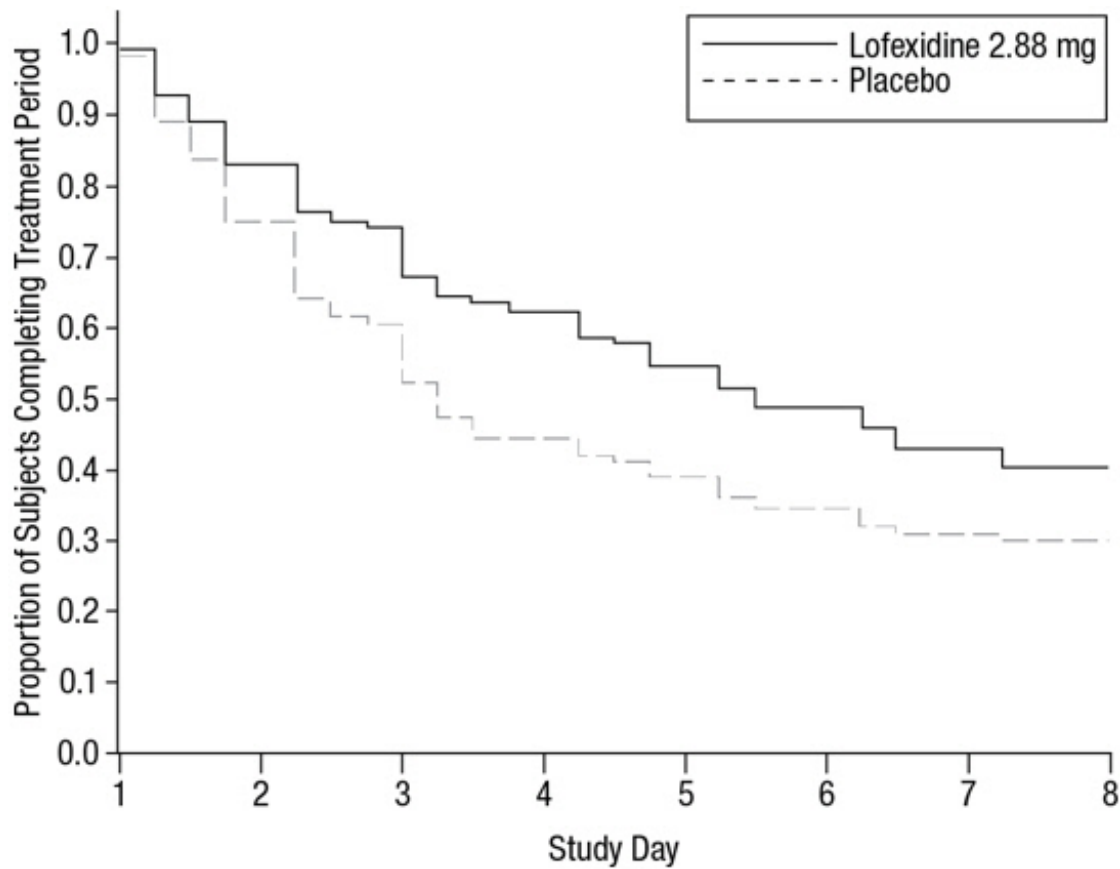
Study 2 was an inpatient, randomized, multicenter, double-blind, placebo-controlled study carried out in the United States in patients meeting DSM-IV criteria for opioid dependence who were physically dependent on short-acting opioids (e.g., heroin, hydrocodone, oxycodone). Patients were treated with LUCEMYRA tablets (2.88 mg/day [0.72 mg 4 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 who 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.

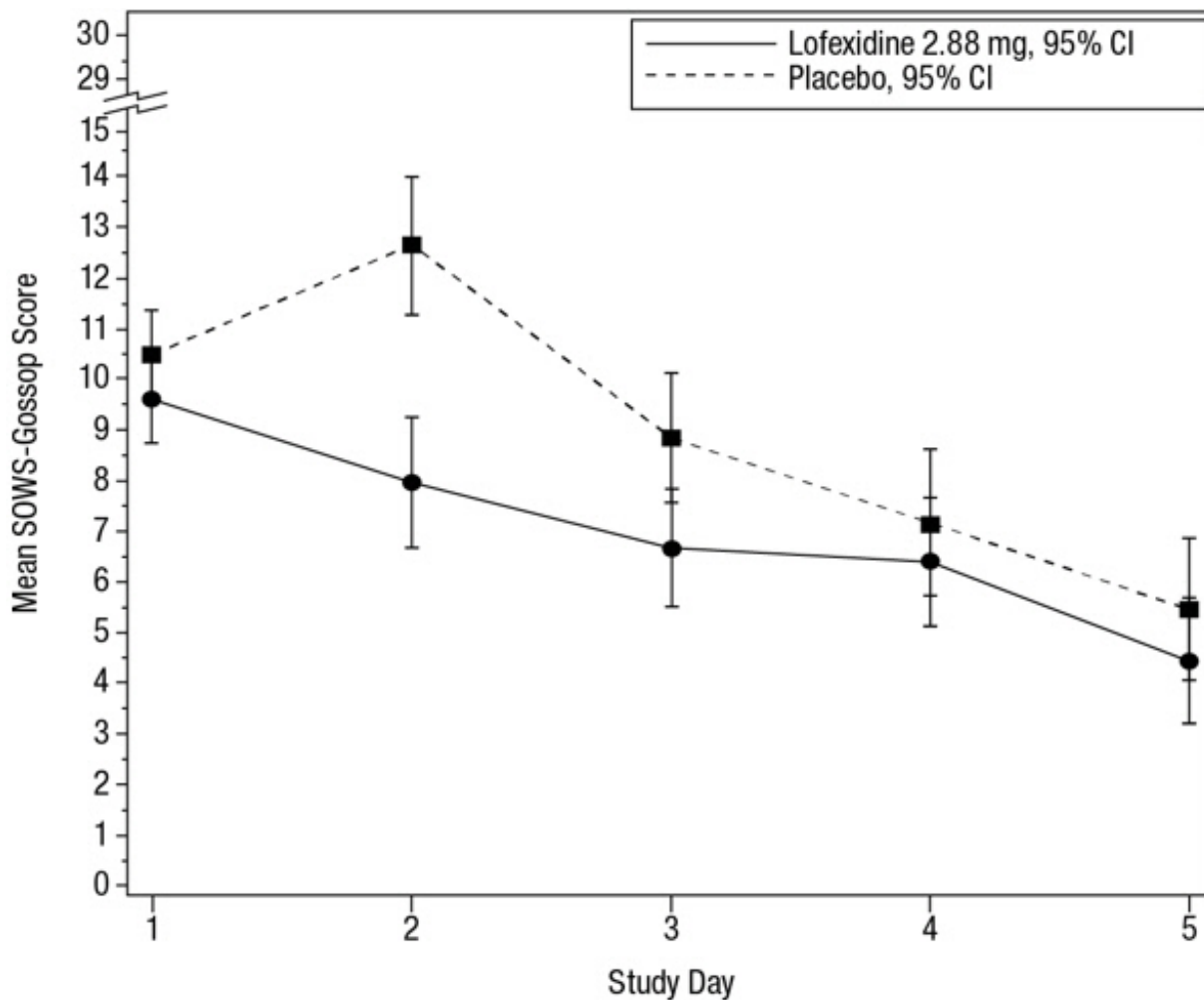
Of the randomized and treated patients, 33% of placebo patients and 49% of LUCEMYRA patients completed 5 days of treatment. The difference in proportion between the two groups was significant. See Figure 3. Patients in the placebo group were more likely to drop out of the study prematurely due to lack 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 78670-050-36

Bottles of 96 tablets NDC 78670-050-96

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 upon 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)*].

This product's Prescribing Information may have been updated. For current full Prescribing Information, please visit www.usworldmeds.com.

Distributed by:
USWM, LLC 4441 Springdale Road
Louisville, KY 40241

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360-10020.01

PATIENT INFORMATION

LUCEMYRA® (LEW-sem-EER-uh)
(lofexidine) tablets

What is the most important information I should know about LUCEMYRA and discontinuing opioid drugs?

LUCEMYRA can cause serious side effects, including low blood pressure (hypotension), slow heart rate (bradycardia), and fainting.

If you have any of the following signs or symptoms, tell your healthcare provider right away:

- low blood pressure
- slow heartbeat
- dizziness
- lightheadedness
- feeling faint at rest or when standing up

If you take LUCEMYRA at home and have any of these signs and symptoms, do not take your next dose of LUCEMYRA until you have talked to your healthcare provider. You should avoid becoming dehydrated or overheated during treatment with LUCEMYRA, which may increase your risk of low blood pressure and fainting. You should also be careful not to stand up too suddenly from lying down or sitting.

When your treatment is complete you will need to stop taking LUCEMYRA gradually or your blood pressure could increase. For more information about side effects, see "**What are the possible side effects of LUCEMYRA?**"

Increased risk of opioid overdose. After a period of time of not using opioid drugs, you can become more sensitive to the effects of opioids if you start using opioids again. This may increase your risk of overdose and death.

What is LUCEMYRA?

LUCEMYRA is a non-opioid prescription medicine used in adults to help with the symptoms of opioid withdrawal that may happen when you stop taking an opioid suddenly.

LUCEMYRA will not completely prevent the symptoms of opioid withdrawal, 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).

LUCEMYRA is not a treatment for opioid use disorder. If you have been diagnosed with opioid use disorder (opioid addiction), your healthcare provider may prescribe LUCEMYRA as part of a complete treatment program for your opioid use disorder (opioid addiction).

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

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

- have low blood pressure
- have a slow heart rate
- have any heart problems, including history of heart attack or a condition

called long QT syndrome

- have liver or kidney problems
- drink alcohol
- are pregnant or plan to become pregnant. It is not known if LUCEMYRA can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if LUCEMYRA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with LUCEMYRA.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, herbal supplements, and any medications you may take for the individual symptoms of opioid withdrawal (such as pain relievers or medications for upset stomach). Especially tell your healthcare provider if you take benzodiazepines, barbiturates, tranquilizers, or sleeping pills. Taking LUCEMYRA with these medicines can cause serious side effects. Ask your healthcare provider or pharmacist if you are not sure if you are taking any of these medicines.

How should I take LUCEMYRA?

- Take LUCEMYRA exactly as your healthcare provider tells you to take it.
- Your healthcare provider may change your dose if needed.
- Do not change your dose or stop taking LUCEMYRA without talking to your healthcare provider.
- Take LUCEMYRA with or without food.
- If you take too much LUCEMYRA, go to the nearest hospital emergency room right away.

What should I avoid while taking LUCEMYRA?

Do not drive, operate heavy machinery, or perform any other dangerous activities until you know how LUCEMYRA affects you.

What are the possible side effects of LUCEMYRA?

The most common side effects of LUCEMYRA include:

- low blood pressure or symptoms of low blood pressure such as lightheadedness
- slow heart rate
- dizziness
- sleepiness
- dry mouth

These are not all the possible side effects of LUCEMYRA.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to US WorldMeds at 1-833-LUCEMYRA.

How should I store LUCEMYRA?

- Store LUCEMYRA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep LUCEMYRA in its original container.
- Keep LUCEMYRA away from heat and moisture.
- LUCEMYRA bottles contain desiccant packs to help keep the tablets dry. Do not remove the desiccant packs until all the tablets are used.

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

General information about the safe and effective use of LUCEMYRA.

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

What are the ingredients of LUCEMYRA?

Active ingredient: lofexidine.

Inactive ingredients: lactose, citric acid, povidone, microcrystalline cellulose, calcium stearate, sodium lauryl sulphate, and Opadry OY S 9480 (contains indigo carmine and sunset yellow).

Distributed by: USWM, LLC, 4441 Springdale Road, Louisville, KY 40241

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USWM, LLC is the exclusive licensee and distributor of LUCEMYRA® in the United States and Its territories.

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For more information, go to www.LUCEMYRA.com or call 1-833-LUCEMYRA

This Patient Information has been approved by the
U.S. Food and Drug Administration.
360-10020.01

Issued: 09/2020

PRINCIPAL DISPLAY PANEL - 0.18 mg Tablet Bottle Carton

Rx only

NDC 78670-050-96

Lucemyra®

(lofexidine) tablets

0.18 mg

Store and dispense
in original container.

Protect from heat and moisture.

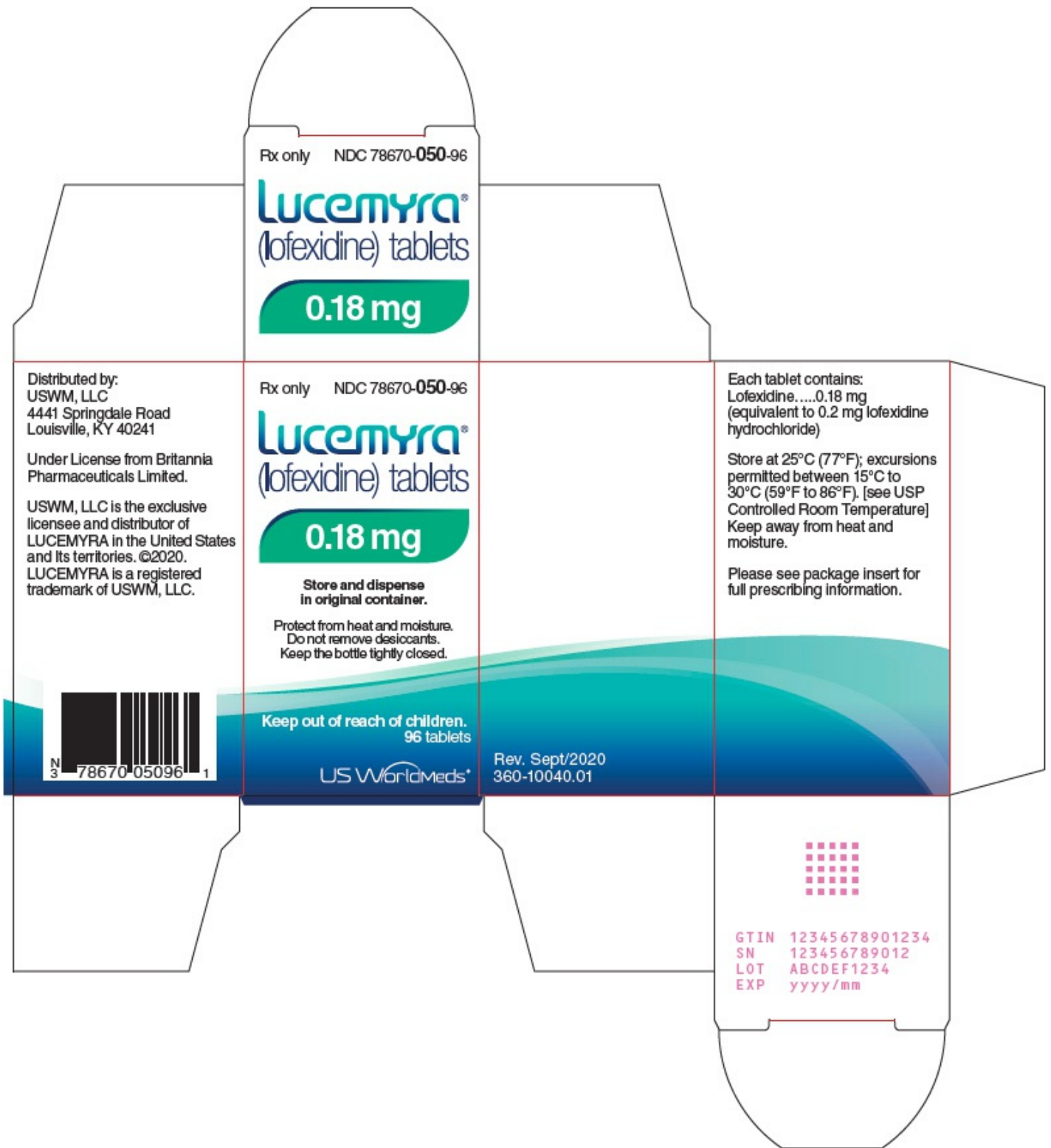
Do not remove desiccants.

Keep the bottle tightly closed.

Keep out of reach of children.

96 tablets

US WorldMeds®



LUCEMYRA

lofexidine hydrochloride tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:78670-050
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LOFEXIDINE HYDROCHLORIDE (UNII: V47G1SDI1B) (LOFEXIDINE - UNII:UI82K0T627)	LOFEXIDINE HYDROCHLORIDE	0.2 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE, UNSPECIFIED FORM (UNII: J2B2A4N98G)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
microcrystalline cellulose (UNII: OP1R32D61U)	
calcium stearate (UNII: 776XM7047L)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	

Product Characteristics

Color	ORANGE (peach)	Score	no score
Shape	ROUND	Size	7mm
Flavor		Imprint Code	LFX;18
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:78670-050-96	1 in 1 CARTON	02/09/2021	
1		96 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:78670-050-36	1 in 1 CARTON	02/09/2021	
2		36 in 1 BOTTLE; Type 0: Not a Combination Product		
3	NDC:78670-050-03	1 in 1 CARTON	02/09/2021	
3		36 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA209229	02/09/2021	

Labeler - USWM, LLC (117542566)**Establishment**

Name	Address	ID/FEI	Business Operations
Catalent Pharma Solutions, LLC		829672745	MANUFACTURE(78670-050) , ANALYSIS (78670-050) , PACK(78670-050)

Establishment

Name	Address	ID/FEI	Business Operations
Acceleration Laboratory Services, Inc		187562629	ANALYSIS(78670-050)

Establishment

Name	Address	ID/FEI	Business Operations
UFAG Laboratoriien AG		486383151	ANALYSIS(78670-050)

Establishment

Name	Address	ID/FEI	Business Operations
Helsinn Birex Pharmaceuticals LTD		985084409	PACK(78670-050)

Establishment

Name	Address	ID/FEI	Business Operations
Apac Packaging LLC		361961142	PACK(78670-050)

Establishment

Name	Address	ID/FEI	Business Operations
A+ Secure Packaging, LLC		963589036	LABEL(78670-050) , PACK(78670-050)

Establishment

Name	Address	ID/FEI	Business Operations
Helsinn Advanced Synthesis SA		481296960	API MANUFACTURE(78670-050) , ANALYSIS(78670-050)