PDL DRUG REVIEW

Proprietary Name: Lucemyra®
Common Name: lofexidine
PDL Category: Opioid Withdrawal Treatments

Comparable Products	Preferred Drug List Status
Clonidine	Preferred

Summary

Pharmacology/Usage: Lofexidine, the active ingredient of Lucemyra®, is a central alpha-2 adrenergic agonist that binds to receptors on adrenergic neurons. This reduces the release of norepinephrine and decreases sympathetic tone.

Indication: For mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults.

There is no pregnancy category for this medication; however, the risk summary indicates that the safety of use in pregnant women has not been established. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 0.18mg

Recommended Dosage: Take 3 tablets PO QID during the period of peak withdrawal symptoms (generally the first 5-7 days after last use of opioid), with dosing guided by symptoms and side effects. There should be 5 to 6 hours between each dose, and the total daily dose should not exceed 2.88mg (16 tablets) and no single dose should exceed 0.72mg (4 tablets). Continue treatment 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). The dose should be reduced, held, or discontinued in those who demonstrate a greater sensitivity to side effects of Lucemyra®. Lower doses may be appropriate as opioid withdrawal symptoms wane.

Stopping treatment abruptly can cause a marked rise in blood pressure. When discontinuing treatment with Lucemyra®, gradually reduce the dose.

Dose adjustments are required for hepatic impairment. With mild impairment (Child-Pugh score 5-6), take 3 tablets QID. With moderate impairment (Child-Pugh score 7-9) take 2 tablets QID. With severe impairment (Child-Pugh >9), take 1 tablet QID. Dose adjustments are required with renal impairment. With moderate impairment (estimated GFR 30-89.9ml/min/1.73m^2), take 2 tablets QID. With severe impairment, ESRD, or on dialysis (eGFR <30ml/min/1.73m^2), take 1 tablet QID.

Drug Interactions: Lucemyra® and methadone both prolong the QT interval**.** If use concomitantly, ECG monitoring is recommended. Concomitant use of oral naltrexone and Lucemyra® resulted in significant differences in the stead-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 given by non-oral routes. Lucemyra® potentiates the CNS depressant effects of benzodiazepines and may potentiate the depressant effect of alcohol, barbiturates, and other sedating drugs. Avoid use in combination with medications that decrease pulse or blood pressure to avoid the risk of excessive bradycardia and hypotension. Monitor for orthostatic hypotension and bradycardia when a CYP2D6 inhibitor is used concomitantly with Lucemyra®.

While the pharmacokinetics of Lucemyra® have not been 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. Monitor adverse events (such as orthostatic hypotension and bradycardia) in known CYP2D6 poor metabolizers. About 8% of Caucasians and 3-8% of Black/African Americans cannot metabolize CYP2D6 substrates and are categorized as poor metabolizers.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Lucemyra® 2.88mg) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than placebo.* The most frequently reported adverse events included insomnia (7%), orthostatic hypotension (37%), bradycardia (27%), hypotension (29%), dizziness (20%), somnolence (8%), sedation (7%), dry mouth (11%), syncope (1.4%), and tinnitus (3.2%).

Lucemyra® can cause a decrease in blood pressure, a decrease in pulse, and syncope. Monitor vital signs before dosing and symptoms related to bradycardia and orthostasis. Patients in an outpatient setting should be educated 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. Lucemyra® may cause hypotension and patients moving from a supine to an upright position may be at increased risk for hypotension and orthostatic effects. Avoid use in patients with severe coronary insufficiency, recent MI, cerebrovascular disease, chronic renal failure, and in patients with marked bradycardia.

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, correct these abnormalities first and monitor ECG upon start of Lucemyra® treatment.

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

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.

Contraindications: There are no contraindications listed with this product.

Manufacturer: US WorldMeds

Analysis: There were 2 randomized, double-blind placebo-controlled studies to assess the safety and efficacy of Lucemyra®.

Study 1 was a 2-part efficacy, safety, and dose-response study conducted in the US that included 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® 2.16mg total daily dose (N=229), Lucemyra® 2.88mg total daily dose (N=222), or matching placebo (N=151). Patients had access to a variety of support medications for withdrawal symptoms. 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 for up to an additional 7 days (days 8-14) in either an inpatient or outpatient setting.

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 is a patient reported outcome instrument that assesses 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 symptom, patients rate their symptom severity using 4 response options, including none, mild, moderate, or severe. 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 patients, 28% of placebo, 41% of Lucemyra® 2.16mg, and 40% of Lucemyra® 2.88mg patients completed 7 days of treatment. The difference in proportion in both Lucemyra® groups was significant compared to placebo. In addition, 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®.

The mean SOWS-Gossop scores for days 1-7 were 8.8 for placebo, 6.5 for Lucemyra® 2.16mg, and 6.1 for Lucemyra® 2.88mg. The mean difference between Lucemyra® 2.16mg and placebo was -2.3, and the mean difference between Lucemyra® 2.88mg and placebo was -2.7. Both differences were 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.

Study 2 was an inpatient, randomized, multicenter, double-blind, placebo-controlled study conducted in the US that included patients meeting DSM-IV criteria for opioid dependence who were physically dependent on short-acting opioids (N=264). Patients were treated with Lucemyra® tablets 2.88mg/day or matching placebo for 5 days (days 1-5). Patients had access to a variety of support medications for withdrawal symptoms. 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 given at baseline and once daily 3.5 hours after the first morning dose on days 1-5. Of the 264 randomized and treated patients, 33% of the placebo group and 49% of the Lucemyra® group completed 5 days of treatment. The difference in proportion between the 2 groups was significant. In addition, 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®.

The mean SOWS-Gossop scores for days 1-5 were 8.9 for placebo and 7.0 for Lucemyra® 2.88mg. The mean difference was -1.9 and was statistically significant.

Place in Therapy: Lucemyra® is indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. It is not a treatment for opioid use disorder. In clinical studies, it was found to significantly reduce the SOWS-Gossop total score as compared with placebo, and significantly more completed treatment with Lucemyra® as compared with placebo.

There is no evidence that Lucemyra® is safer or more effective than the currently available, more cost-effective medications. It is therefore recommended that Lucemyra® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Lucemyra [package insert]. Louisville, KY: US WorldMeds, LLC; 2018.

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