CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213378Orig1s000
213378Orig2s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	213378
PDUFA Goal Date	November 15, 2020
OSE RCM #	2019-2354
Reviewer Name(s)	Leah Hart, PharmD
Team Leader	Carolyn Tieu, PharmD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	November 13, 2020
Subject	Evaluation of Need for a REMS
Established Name	Olanzapine/Samidorphan
Trade Name	Lybalvi
Name of Applicant	Alkermes Inc
Therapeutic Class	Antipsychotic /μ receptor antagonist
Formulation(s)	Oral tablets
Dosing Regimen	Schizophrenia: Start at 5 mg/10 mg or 10 mg/10 mg Bipolar I disorder (manic or mixed episodes): Start at 10 mg/10 mg or 15 mg/10 mg. For both: The recommended dose is 10 mg/10 mg, 15 mg/10 mg or 20 mg/10 mg, once daily as a single tablet

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Lybalvi (olanzapine and samidorphan) is necessary to ensure the benefits outweigh its risks. Alkermes Inc (Alkermes) submitted a New Drug Application (NDA) 213378 for Lybalvi with the proposed indication to treat schizophrenia, manic and mixed episodes of bipolar I disorder, and for maintenance of bipolar I disorder. The Applicant did not submit a REMS with this application but proposed voluntary risk management activities consisting of a communication plan that includes materials for both healthcare providers and patients.

Adverse events associated with Lybalvi were largely similar to those of olanzapine which are currently communicated through labeling. Like other antipsychotics, Lybalvi will contain a boxed warning for the risk of increased mortality in elderly patients with dementia-related psychosis. Samidorphan is an opioid antagonist, an NME and a component of Lybalvi. Lybalvi and samidorphan are not currently approved in any jurisdiction. Due to the samidorphan, the risks in patients receiving opioids include precipitation of opioid withdrawal and potential vulnerability to opioid overdose. Labeling will include that Lybalvi is contraindicated in patients using opioids. Warnings and Precautions will include that Lybalvi should not be administered to patients taking chronic opioids and that prescribers should consider alternative treatments to Lybalvi, such as olanzapine in patients who need short term treatment with an opioid. Although not observed in the clinical trials, patients may be more sensitive to opioids if the samidorphan is discontinued and could be at risk for an opioid overdose.

If approved, DRM has determined that a REMS is not needed to ensure the benefits of Lybalvi outweigh its risks. We believe that labeling will be able to communicate the risks associated with Lybalvi to prescribers and should aid them in appropriate patient selection. In addition, we plan to consult with other offices in the Center for Drug Evaluation and Research such as the Professional Affairs and Stakeholder Engagement to engage external stakeholders about how to communicate these risks to other healthcare providers who may not prescribe Lybalvi.

The clinical reviewer concluded that the benefit of Lybalvi outweigh its risks for the treatment of schizophrenia and bipolar I disorder in adults. However, the review team recommends a complete response due to manufacturing concerns.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Lybalvi (olanzapine and samidorphan) is necessary to ensure the benefits outweigh its risks. Although olanzapine is currently approved, samidorphan is an NME and has not been approved in the US. Alkermes Inc (Alkermes) submitted a New Drug Application (NDA) 213378 for Lybalvi with the proposed indication to treat schizophrenia, manic and mixed episodes of bipolar I disorder, and for maintenance of bipolar I disorder. This application is under review in the Division of Psychiatry (DP). The Applicant did not submit a REMS with this application but proposed voluntary risk management activities.

2 Background

2.1 PRODUCT INFORMATION

Lybalvi (olanzapine/samidorphan) is an oral, fixed dose combination of olanzapine and samidorphan (olan/sam) for the treatment of schizophrenia, manic and mixed episodes of bipolar I disorder, and for maintenance of bipolar I disorder. Olanzapine is an atypical antipsychotic approved in 1996 for the treatment of the manifestations of psychotic disorders and currently approved orally for the treatment of schizophrenia, acute treatment of manic or mixed episodes associated with bipolar I disorder, and maintenance treatment of bipolar I disorder. Samidorphan, an NME[a], is a μ opioid-receptor antagonist intended to mitigate olanzapine-induced weight gain. The Applicant hypothesizes that combining samidorphan with olanzapine will reduce the weight gain and metabolic adverse reactions commonly associated with olanzapine use while continuing to deliver the therapeutic antipsychotic benefits of olanzapine. The proposed indication for Lybalvi is the treatment of schizophrenia and bipolar I disorder. For bipolar I disorder, the indication is for both monotherapy for acute treatment of manic or mixed episodes and maintenance treatment, or adjunctive therapy to lithium or valproate in the treatment of manic or mixed episodes.[b] Lybalvi, if approved, will be available as 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg, and 20 mg/10 mg tablets for oral administration. Samidorphan has a blood half-life (t ½) of 7-11 hours. Lybalvi nor samidorphan is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 213378 relevant to this review:

- 11/15/2019: NDA 213378 submission for the treatment of schizophrenia and bipolar I disorder received
- 05/14/2020: A post mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that would require a REMS for Lybalvi.
- 08/05/2020: The Agency communicated the rationale to the Applicant for including the Drug Safety and Risk Management Advisory Committee on 10/09/2020.
- 08/26/2020: Applicant provided a response to the Agency's 08/05/2020 communication outlining voluntary risk management activities to mitigate the risks of precipitated opioid withdrawal in patients using opioids, potential for opioid overdose in patients who use high doses of opioids for acute pain or nonmedically in attempts to overcome samidorphan's opioid blockade, potential for opioid overdose if patients resume a previous dose of opioids after discontinuing olanzapine/samidorphan, and the potential for inadequate analgesia when analgesia is medically required.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 10/09/2020: A joint meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee was convened to discuss the safety and efficacy of Lybalvi. The AC voted 16 yes and 1 no, that there was adequate evidence that samidorphan meaningfully mitigates olanzapine-associated weight gain. A REMS was discussed, but the AC voted 11 yes and 6 no that labeling is sufficient to mitigate the risks related to the opioid antagonist action of samidorphan.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Schizophrenia

Schizophrenia is a psychiatric disorder involving chronic or recurrent psychosis and is one of the top 15 leading causes of disability worldwide.[1] Schizophrenia is typically diagnosed in the late teens to early thirties and tends to emerge earlier in males.[2] Estimates of the prevalence of schizophrenia range between 0.25% to 0.75%.[3,c]

People with schizophrenia often present with several symptom domains- positive symptoms, negative symptoms, cognitive impairment, and/or mood and anxiety symptoms.[4,5,6] Positive symptoms represent an exaggeration of normal processes and include hallucinations and delusions, as well as disorganized thoughts and behavior. Negative symptoms are an absence or diminution of normal processes and can be categorized into primary or secondary. Primary negative symptoms, or deficit symptoms, include decreased expressiveness, apathy, flat affect, and a lack of energy. Secondary negative symptoms can be caused by depression, psychotic symptoms, medication side effects, and substance abuse, and they usually improve with treatment of the underlying cause. Cognitive impairments can include decreased processing speed, attention, memory, reasoning, verbal comprehension, and social cognition. These changes in cognition may precede the actual diagnosis, often by years. Schizophrenia can also have physical manifestations including neurological disturbances, catatonia, and metabolic disturbances. Schizophrenia is associated with diabetes, dyslipidemia, and hypertension. These can be due to medication or other risk factors, including a sedentary lifestyle and smoking. The life expectancy of people with schizophrenia is reduced by more than a decade compared with the general population and largely due to heart disease.[7,d] An estimated 4.9% of people with the disease die by suicide, a rate that is far greater than the general population, with the highest risk in the early stages of illness.[8]

Bipolar Disorder

Bipolar disorder is a mood disorder that is characterized by episodes of mania, hypomania, and major depression.[9] Patients with bipolar I disorder experience manic episodes and nearly always experience

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

major depressive and hypomanic episodes. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) stipulates that the mood episodes in bipolar I disorder are not better accounted for by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder. Most bipolar patients have at least one other psychiatric disorder. The lifetime prevalence of at least one co-occurring disorder was 92%[10] as compared to 46%[11] in the general population. This co-occurring disorders can include anxiety disorders, attention deficit hyperactivity disorder, eating disorders, intermittent explosive disorders, obsessive-compulsive disorder, personality disorders, borderline personality disorder, and substance use disorders.

An estimated 10-15% of bipolar patients die by suicide and approximately 15 times the expected value.[12,13] In 2015, the total costs associated with bipolar I disorder were estimated at 202.1 billion dollars, corresponding to an average of 48,333 dollars per individual. Out of the 202.1 billion, the majority of costs are due to caregiving (36%), direct healthcare costs (21%), and unemployment (20%).[14]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Schizophrenia

The most recent American Psychological Association (APA) practice guideline for the treatment of schizophrenia recommends three treatment goals: 1) to reduce or eliminate symptoms, 2) maximize the quality of life and adaptive functioning, and 3) promote and maintain recovery from the debilitating effects of illness to the maximum extent possible.[15] Schizophrenia has an acute stage, a stabilization phase, and stable phase. Across all stages of schizophrenia, treatment with antipsychotic medication is indicated for nearly all episodes of acute psychosis in patients with schizophrenia. The agent used will depend on the potential risks and benefits of various antipsychotics. Antipsychotic medications are categorized in the following ways: first-generation agents (e.g. haloperidol, loxapine, thioridazine), and second-generation agents (e.g. aripiprazole, olanzapine). The selection of an antipsychotic medication is frequently guided by the patient's previous experience with antipsychotics, including the degree of symptom response, the side effect profile (including past experience of side effects such as dysphoria), and the patient's preferences for a particular medication, including the route of administration. The second-generation antipsychotics should be considered as first-line medications for patients in the acute phase of schizophrenia, mainly because of the decreased risk of extrapyramidal side effects and tardive dyskinesia. Non-pharmacological therapies include electro-convulsion therapy (ECT) and may be considered for patients who have not responded to treatment with antipsychotic agents. Antipsychotics can reduce the risk of relapse in the stable phase of illness to less than 30% per year.[16] Without maintenance treatment, 60%–70% of patients relapse within 1 year, and almost 90% relapse within 2 years.[17]

Bipolar I Disorder

For acute treatment of bipolar I disorder, the most recent APA guideline's recommendations are based on whether the patient experiences manic or mixed episodes, and/or depressive episodes.[18] The first-line pharmacological treatment for more severe manic or mixed episodes is the initiation of either lithium plus an antipsychotic or valproate plus an antipsychotic. For less ill patients, monotherapy with

lithium, valproate, or an antipsychotic should be sufficient. For mixed episodes, valproate may be preferred over lithium. Atypical antipsychotics are preferred over typical antipsychotics because of their more benign side effect profile, with most of the evidence supporting the use of olanzapine or risperidone. Alternatives include carbamazepine or oxcarbazepine in lieu of lithium or valproate. When first-line medication treatment at optimal doses fails to control symptoms, recommended treatment options include addition of another first-line medication. Alternative treatment options include adding carbamazepine or oxcarbazepine in lieu of an additional first-line medication, adding an antipsychotic if not already prescribed, or changing from one antipsychotic to another. Clozapine may be particularly effective in the treatment of refractory illness. The first-line pharmacological treatment for bipolar depression is the initiation of either lithium or lamotrigine. Antidepressant monotherapy is not recommended. As an alternative, especially for more severely ill patients, some clinicians will initiate simultaneous treatment with lithium and an antidepressant. When an acute depressive episode of bipolar disorder does not respond to first-line medication treatment at optimal doses, next steps include adding lamotrigine, bupropion, or paroxetine. Alternative next steps include adding other newer antidepressants (e.g., a selective serotonin reuptake inhibitor [SSRI] or venlafaxine) or a monoamine oxidase inhibitor (MAOI). Nonpharmacological therapy includes ECT and may be considered for patients with life-threatening inanition, suicidality, or psychosis.

In both schizophrenia and bipolar I, once the patient is in the maintenance phase, patients with bipolar disorder are likely to benefit from a concomitant psychosocial intervention—including psychotherapy—that addresses illness management (i.e., adherence, lifestyle changes, and early detection of prodromal symptoms) and interpersonal difficulties.

A summary of treatment options relevant to the proposed indication can be found in Appendix 10.1.

Atypical antipsychotics have been associated with metabolic changes that include hyperglycemia, diabetes mellitus, dyslipidemia, and body weight gain. Each drug has its own risk profile. These risks are well-described sequelae of olanzapine and other atypical antipsychotics that contribute to lack of compliance with treatment and cardiometabolic disease burden in this vulnerable patient population. Olanzapine in particular has been associated with these adverse events which are included in labeling. In a 2005 study of almost 1500 patients with schizophrenia randomized to olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone for up to 18 months, patients treated with olanzapine were generally less likely to discontinue treatment for any cause (a surrogate for antipsychotic efficacy); however, significantly more patients on olanzapine discontinued drug due to adverse events, primarily due to weight gain and metabolic effects (9% vs. 1% to 4% for the other drugs).[19] In one study, among 669 patients receiving olanzapine analyzed, approximately 39% of patients who gained 2 kg or more at week 3 experienced a weight gain of 10 kg or more by week 30, while approximately 12% of patients who gained less than 2 kg by week 3 experienced a weight gain of 10 kg or more by week 30.[15]

4 Benefit Assessment

The benefit assessment is summarized from the integrated clinical review. Refer to the integrated review for additional information.

Schizophrenia

The efficacy of Lybalvi in the treatment of schizophrenia was demonstrated in a 4-week, randomized, double-blind, placebo- and active-controlled study (Study 1; A305). A second 24-week, randomized, double-blind, active-controlled study (Study 2; A303) demonstrated less weight gain with Lybalvi relative to olanzapine in adults with schizophrenia.

Study 1 (A305) is a randomized, double-blind, multinational, multicenter, parallel-group, placebo-controlled inpatient design comparing two doses of olan/sam (10/10 mg daily and 20/10 mg daily) to olanzapine (10 mg daily and 20 mg daily) and placebo over a 4-week treatment period. The subjects were ages 18 to 70 years who were diagnosed with schizophrenia and experiencing an acute exacerbation. The primary endpoint was a change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at week 4. The secondary endpoint was the change from baseline in Clinical Global Impression of Severity Scale (CGI-S) at week 4. Four hundred and three subjects randomized, and 352 subjects completed the study. Treatment with olan/sam was associated with improvement in schizophrenia symptoms. For the primary endpoint, the least squares (LS) mean change from baseline PANSS total score was -17.5 in the placebo group, -23.9 in the olan/sam group, and -22.8 in the olanzapine group; LS mean difference between olan/sam and placebo treatment was -6.4 with a 95% CI (-10.2, -2.8). The primary efficacy analysis of the primary efficacy endpoint showed a statistically significant difference of olan/sam in comparison to placebo, in LS mean change from baseline in PANSS total score at Week 4. A comparison of olanzapine with placebo suggested a similar treatment effect to olan/sam. With respect to the secondary endpoint (change in CGI-S from baseline to week 4), olan/sam showed a statistically significantly difference from placebo, supporting the findings from the primary efficacy endpoint although the observed treatment difference (point estimate = -0.38 and 95% CI (-0.61, -0.14)) was relatively small. Olanzapine also showed similar effects.

Study 2 (A303) is a multicenter (U.S.-only), olanzapine-controlled, randomized, double-blind, study in adults with schizophrenia. The primary objective was to evaluate weight gain with olan/sam compared to olanzapine; the secondary objective was to evaluate the safety and tolerability of olan/sam; an exploratory objective was to evaluate subject's body composition at the beginning of the 24 weeks and the end of treatment. Subjects were randomized 1:1 to receive 10 mg/10 mg or 20 mg/10 mg of olan/sam or olanzapine 10 mg or 20 mg. The co-primary endpoints were to evaluate the percent change in body weight from baseline to week 24 and the proportion of subjects with >10% weight gain at week 24. The secondary endpoint was the proportion of subjects with >7% weight gain at week 24. Five hundred sixty-one were randomized with 550 included in the safety population who received at least one dose of study drug, and 352 subjects who completed the study. The first coprimary endpoint, percent change from baseline in weight at week 24, was significantly lower in patients treated with olan/sam than in patients treated with olanzapine (p =0.003). The treatment effect estimate (difference in mean percent weight change from baseline between olan/sam and olanzapine) was -2.38% (95% CI: -3.88%, -0.88%), favoring olan/sam. The second coprimary endpoint, proportion of subjects who had $\geq$ 10% increase in weight from baseline to week 24, was significantly lower in subjects treated with olan/sam (p=0.003). The odds ratio (olan/sam compared to olanzapine) for having a 10% or greater increase in weight from baseline to Week 24 was 0.50 (95% CI: 0.31, 0.80). The proportion of patients

who gained 10% or more weight from their baseline was significantly lower for olan/sam (17.8%) than for olanzapine (29.9%), with an absolute 13.7% difference between the groups (95% CI: -22.8%, -4.6%). With regards to the key secondary endpoint, proportion of subjects who had ≥7% increase in weight from baseline to week 24, was significantly lower in subjects treated with olan/sam than in subjects treated with olanzapine (p = 0.001, unadjusted for sample size increase).

Metabolic changes were assessed in Study A303. Mean lipid changes were similar between groups, with an apparent small attenuation of the rise in total cholesterol and triglycerides (TG) with olan/sam at some visits. At week 2 there was a small increase in LDL cholesterol (LDL-C) in the olan/sam group as compared to olanzapine of unclear clinical significance. In patients treated with olan/sam, there was a trend of increased fasting glucose as compared to olanzapine. Conversely, there was a decrease in hemoglobin A1c (HbA1c) vs. olanzapine at Week 20, but no difference at other timepoints. There were no differences in fasting insulin between groups. The Applicant reported in a post hoc analysis that the LS mean difference between olan/sam and olanzapine in systolic and diastolic blood pressure (BP) in mm Hg at week 24 was -2.60 (95% CI -4.73, -0.47) and -0.70 (95% CI -2.23, 0.84), respectively. In addition, a figure of blood pressure over time suggests that the separation between groups in systolic BP is seen by week 4 and persisted across the double-blind treatment period. No consistent differences between groups were observed in diastolic BP.

Bipolar I Disorder

The safety and efficacy of olan/sam has not been studied in subjects with bipolar I disorder. The bipolar I disorder indication is based on a pharmacokinetic bridge to olanzapine.

The clinical reviewer concluded that olan/sam demonstrated antipsychotic efficacy and statistically significant weight mitigation effect and there was suggested favorable difference in systolic blood pressure changes. Refer to the integrated review for additional information.

5 Risk Assessment & Safe-Use Conditions

Olan/sam safety pool consists of 1601 subjects who received at least one dose of olan/sam (this does not include ongoing studies) and 557 subjects who have received at least one dose of samidorphan.[20] Commonly reported AEs occurring in ≥5% of subjects receiving olan/sam included: weight increased, somnolence, dry mouth, headache, anxiety, increased appetite, fatigue, infection, waist circumference increased, upper respiratory infection, extra dose administered, and blood creatinine kinase increased. Rates for these AEs were generally similar for both olan/sam and olanzapine groups, except in study A303, somnolence, dry mouth and fatigue occurred more frequently with olan/sam treatment. Rates of serious adverse events (SAEs) and AEs leading to study discontinuation were similar between the two treatment groups.

Three deaths occurred in the development program, but all were unlikely related to treatment. One subject randomized to the treatment group in a phase 2 study died secondary to chronic obstructive pulmonary disease (COPD) and another as a result of alcohol poisoning. The third subject was in a phase 3 study randomized to olanzapine and died secondary to heroin overdose.

Overall, 19 subjects (2%) out of 951 experienced SAEs in studies A305 and A303. In study A305 two subjects experienced SAEs but both were unlikely to be related to the study drug. There were 17 subjects in study A303 that experienced SAEs. SAEs occurring in more than one subject were schizophrenia and drug abuse. Drug abuse occurred in two subjects randomized to olan/sam, however the incidence of any drug abuse TEAE was equal between both treatment groups (1%).

Because of samidorphan's opioid antagonist action, other potential safety risks with concurrent opioid use include precipitated withdrawal, ineffective analgesia, and opioid overdose. Because opioid use was an exclusion criterion in the clinical development, assessment of these safety risks was limited. Epidemiology studies were reviewed by the Division of Epidemiology (DEPI) and Division of Pharmacovigilance to provide context for the overall-benefit/risk assessment of samidorphan. These safety risks are described below.

5.1 PATIENTS RECEIVING OPIOIDS

Precipitation of Opioid Withdrawal

An event of opioid withdrawal was reported in a Phase 1 study. The subject did not disclose his long-term opioid dependence, which would have excluded him from the study. His symptoms of withdrawal began two minutes after administration of samidorphan and subsequently received treatment during hospital admission. In the Study 1; A305 and Study 2; A303, there were no acute opioid withdrawal reported and subjects were required to be opioid-free for 14 days prior to initiating olanzapine/samidorphan.

Epidemiologic studies show an association between bipolar disorder and chronic pain conditions.[21] In one U.S. study, the percentage of patients with bipolar disorder who reported chronic opioid use was three times higher than patients without bipolar disorder.[22] Epidemiology data also suggest a higher prevalence of nonmedical opioid use and opioid use disorder in people with bipolar disorder relative to the general population. Considering the estimated prevalence of nonmedical opioid use (3.6%) or opioid use disorder (0.7%) in the general U.S. population[23], the DEPI reviewers estimate that the percentage of individuals with bipolar disorder who use opioids nonmedically in a given year may be greater than 5%, and the percentage of individuals with bipolar disorder who have an opioid use disorder may be in the range of 1 to 3%, depending on other characteristics of the patient population.[e,24]

Data are sparse on nonmedical opioid use and opioid use disorder in patients with schizophrenia. Older survey data suggest that the percentage of individuals with schizophrenia who use opioids nonmedically may be greater than in patients without mental illness.

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

DEPI further analyzed drug utilization data and found that among patients with olanzapine prescription claims in 2019, approximately 21% had concurrent opioid prescription claims, either as analgesics or cough/cold products.[25]

Another fixed dose, combination product that contains an opioid antagonist, Contrave (bupropion/naloxone), was approved on September 10, 2014, for chronic weight management adjunct to a reduced-calorie diet and increased physical activity. In the 2017 Pharmacovigilance I review of postmarket cases in FDA Adverse Event Reporting System (FAERS) and the National Poison Data System (NPDS) identified adverse events potentially related to opioid withdrawal reportedly occurring when an approved, naltrexone-containing product (bupropion/naltrexone) was used with an opioid.[25] At the time of the review, just over two years of postmarketing data were available, yielding 69 cases in FAERS and 22 cases in NPDS. The majority of the cases were mild, but there were a few cases of more severe events such as seizures that required hospitalization. The review also included one case report of reduced acute opioid analgesic effect.[26] An updated Pharmacovigilance memo included cases from December 2017 to August 2020. There were 13 cases of suspected opioid withdrawal, two of which required hospitalization.[27] There is some evidence to suggest that in a population not currently being treated for opioid use disorder, adverse events potentially related to opioid withdrawal can occur when an opioid-antagonist-containing product is used in the setting of opioid use.

Although there were limited data during clinical trial to assess these potential safety risks related to the opioid antagonism of the samidorphan component, epidemiology data suggests these risks may be occurring in real-world settings. Therefore, the prescribing information (PI) will contraindicate use of Lybalvi in patients who are using opioids. Warnings and precautions of the proposed labeling will also warns that those who are physiologically dependent on opioids should be opioid-free prior to starting treatment.[28] If a rapid transition to olanzapine/samidorphan is deemed necessary and appropriate, the healthcare provider will be advised to monitor the patient closely in an appropriate medical setting where precipitated opioid withdrawal can be managed.

Vulnerability to opioid overdose

Although not seen in the clinical development program, patients could be vulnerable to opioid overdose. Theoretically, samidorphan could lead to ineffective analgesia when opioids are medically necessary or in patients with an opioid use disorder. Attempts to overcome samidorphan's opioid antagonist effects could lead to administration of greater amounts of opioids which could lead to an overdose if the samidorphan effect wanes or fluctuates (i.e., with discontinuation or missed doses), exposing the patient to a high level of unopposed opioid agonist.

The Applicant did not conduct samidorphan receptor occupancy studies, therefore it is unknown if the binding is competitive or non-competitive and can be displaced by administration of an opioid. Although samidorphan has a blood half-life (t ½) of 7-11 hours with drug levels falling to <10 ng/mL by 24 hours, the duration of receptor occupancy will depend on the location of the receptors. If they are within the central nervous system (CNS), the drug levels as well as the t ½ may be different in the CNS versus blood. This unknown duration of receptor occupancy makes determining the time at which an overdose could occur difficult.

The 2017 Pharmacovigilance I review, also found that 11% of patients on Contrave had a concurrent claim of opioid products despite their contradiction in labeling. Due to the limitation in the data sources, the review was unable to determine the reason for co-prescribing Contrave and an opioid product. Notably, the concurrency analysis used national projections generated from outpatient retail dispensing claims, and outcome data were not available. Therefore, the reviewers could not determine the actual risk of opioid overdose in these patients. Individuals prescribed Lybalvi and use opioids, could theoretically be at risk for overdose if they attempt to overcome samidorphan's opioid blockade and Lybalvi is stopped or interrupted.

Due to the samidorphan component of Lybalvi, the warnings and precautions section of the proposed labeling will include that Lybalvi should not be administered to patients receiving chronic opioids. If chronic opioid therapy is required, Lybalvi treatment should be stopped. Patients may experience reduce or ineffective analgesia. If patients require short-term opioid treatment, providers should consider olanzapine or another antipsychotic until the need for opioid treatment is resolved. The label warns that an attempt to overcome the opioid blockade may lead to a fatal overdose or life-threatening opioid intoxication. This warning and precaution also states that patients should be alerted that they may be more sensitive to opioids, even at lower doses, after Lybalvi treatment is discontinued and that patients should be told of the serious consequences of trying to overcome the opioid blockade.

6 Expected Postmarket Use

Lybalvi will be used in both outpatient and inpatient settings as a long-term medication. The likely prescribers are psychiatrists. Prescribers will play a pivotal role in managing the risks outlined in sections 5 of this review. Psychiatrists are familiar with treating schizophrenia and bipolar I disorder and are also likely to be familiar with opioid use disorder.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not submit a REMS but proposed voluntary risk management activities to address the risks of precipitated opioid withdrawal, fatal overdose, and inadequate pain control. Their proposed risk management activities include (b) (4)

We do not object the to the proposed voluntary risk management activities; however, as these materials are not part of labeling or a REMS, they should be reviewed by the Office of Prescription Drug Promotion.

8 Discussion of Need for a REMS

Lybalvi is an oral, fixed dose combination of olanzapine and samidorphan (5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg, and 20 mg/10 m) for the proposed treatment of schizophrenia and bipolar I disorder in adults. Samidorphan, is an NME, a μ opioid-receptor antagonist intended to mitigate olanzapine-induced weight gain.

AEs associated with Lybalvi were largely similar to those of olanzapine which are currently communicated through labeling. Because of the samidorphan component, Lybalvi also has the potential to cause opioid withdrawal in patients who are using opioids prior to starting Lybalvi and patients could be vulnerable to opioid overdose that concomitantly use Lybalvi and an opioid. Since patients with opioid use were excluded during the clinical development, assessment of these safety risks was limited during clinical trials. To assess these potential safety risks in real world settings, epidemiologic literature was reviewed which suggests that these risks may occur in postmarket settings in the indicated population. Appropriate patient selection for Lybalvi should be considered.

The risk of precipitating of acute opioid withdrawal and the theoretical risk of vulnerability to opioid overdose were discussed during the joint meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee on October 9, 2020. When asked if the safety profile for Lybalvi had been adequately characterized for Lybalvi, 13 committee members voted yes and 3 voted no and one abstained. When asked if the labeling was sufficient to mitigate the risks associated with the use of Lybalvi, 11 committee members voted yes and 6 voted no. During the advisory meeting, some members expressed concerns about healthcare providers who will not prescribe Lybalvi, but may prescribe an opioid (e.g., dentists or emergency room physicians) to a patient receiving Lybalvi. These prescribers may not be aware that Lybalvi contains a new opioid antagonist. A few panel members questioned if a REMS should be utilized to communicate risks to the prescribers of opioids.

The Applicant has proposed to mitigate the risks through labeling, including a contraindication in patients using opioids, warnings and precautions, and a Medication Guide. The Applicant did not propose a boxed warning for the risks of opioid withdrawal or vulnerability to opioid overdose. The review team did discuss on multiple occasions the best way to communicate the theoretical risk of vulnerability to opioid overdose in labeling. In reviewing other product labels that contain an opioid-antagonist, warnings and precautions are used to communicate these risks. Similar to other products that contain an opioid-antagonist, warnings and precautions will be used to communicate this risk for Lybalvi. The Applicant is also proposing a voluntary risk management activity which includes a communication plan that would include (b) (4)

The review team discussed several ways to communicate the risks of opioid withdrawal or vulnerability to opioid overdose to health care providers who may prescribe opioids, including the possibility of a Communication Plan (CP) REMS. As with any newly approved product, the prescriber should be aware of the benefits and the risks and should consider if the product is appropriate for an individual patient. We believe that labeling will be able to communicate these risks to prescribers and should aid them in appropriate patient selection, such that Lybalvi may not be an appropriate choice for patients that use opioids or have chronic pain needs that require an opioid. A CP REMS would typically target the likely

prescribers (psychiatrist) of Lybalvi. The concerns expressed by the Advisory Committee were not with the likely prescribers of Lybalvi but rather health providers who may prescribe an opioid to a patient who is receiving Lybalvi. The review team concluded that a CP REMS may not be able to effectively reach healthcare providers who might prescribe an opioid to a patient taking Lybalvi. We do believe that labeling is sufficient to communicate the safety risks; however, it would be helpful to have additional communications regarding the risks of opioid withdrawal and vulnerability to opioid overdose to healthcare providers who prescribe opioids and professional organizations. We plan to consult with other offices in Center of Drug Evaluation and Research such as the Professional Affairs and Stakeholder Engagement to engage external stakeholders about how to communicate these risks to other healthcare providers who may not prescribe Lybalvi.

The clinical reviewer concluded that the benefit of Lybalvi outweigh its risks for the treatment of schizophrenia and bipolar I disorder in adults. However, the review team recommends a complete response due to manufacturing concerns. Refer to the integrated review for more additional information.

9 Conclusion & Recommendations

Based on the initial clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Lybalvi to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 Table 1. Summary of Treatment Options For Schizophrenia and Bipolar Disorder

Product Trade Name (Generic) Year of Approval	Indication	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
FDA Approved Treatments				
Abilify (Aripiprazole) 2002	Schizophrenia Bipolar disorder (manic and mixed episodes and maintenance)	Oral- 10-15 mg once daily IM- 9.75 mg max daily dose 30 mg at least 2 hours apart	Warnings and Precautions (W&P): Metabolic changes including hyperglycemia, dyslipidemia, and weight gain	Both- Boxed Warning (BW) for increased mortality in elderly patients with dementia-related psychosis; Medication Guide (MG)
Aristada (Aripiprazole) 2015	Schizophrenia	IM- 441 mg, 662 mg or 882 mg administered monthly, 882 mg dose every 6 weeks, or 1064 mg dose every 2 months	W&P: Metabolic changes including hyperglycemia, dyslipidemia, and weight gain	BW for increased mortality in elderly patients with dementia-related psychosis; MG
Saphris (Asenapine) 2009	Schizophrenia Bipolar disorder (manic and mixed episodes and maintenance	Oral- 5-10 mg twice daily	W&P: Metabolic changes including hyperglycemia, dyslipidemia, and weight gain	BW for increased mortality in elderly patients with dementia-related psychosis
Secuado (Asenapine) 2019	Schizophrenia	Transdermal patch- 3.8 mg/24 hours. May increase dosage to 5.7 mg/24 hours or 7.6 mg/24 hours after one week	W&P: Metabolic changes including hyperglycemia, dyslipidemia, and weight gain	BW for increased mortality in elderly patients with dementia-related psychosis
Rexulti (Brexpiprazole) 2015	Schizophrenia	Oral- 1-4 mg once daily	W&P: Metabolic changes including hyperglycemia, dyslipidemia, and weight gain	BW for increased mortality in elderly patients with dementia-related psychosis; MG
Vraylar (Cariprazine) 2015	Schizophrenia Bipolar disorder (manic, mixed, and depressive episodes)	Oral- 1.5-6 mg once daily	W&P: Metabolic changes including hyperglycemia, dyslipidemia, and weight gain	BW for increased mortality in elderly patients with dementia-related psychosis and antidepressants increased risk of suicidal thoughts and behaviors in pediatric and young adult patients; MG

Thorazine (Chlorpromazine) 1957	Schizophrenia	Oral- starting dose 10-25 mg two to four times daily depending on severity of symptoms; little therapeutic gain achieved >1000 mg. IM- 25 mg, if necessary, give additional 25 to 50 mg	Warnings- Tardive dyskinesia (TD), neuroleptic malignant syndrome (NMS)	BW for increased mortality in elderly patients with dementia-related psychosis; MG
Clozaril (Clozapine) 1989	Schizophrenia	12.5 mg once daily or twice daily with a target dose of 300 mg – 450 mg per day in divided doses; max daily dose 900 mg	W&P: Metabolic changes including hyperglycemia, dyslipidemia, and weight gain	REMS for severe neutropenia; BW for severe neutropenia; orthostatic hypotension, bradycardia, and severe syncope; seizure, myocarditis and cardiomyopathy; increased mortality in elderly patients with dementia-related psychosis
Depakote (Divalproex) 1983	Bipolar disorder (manic episodes)	Initial dose is 750 mg daily, increasing as rapidly as possible to achieve therapeutic response or desired plasma level. The maximum recommended dosage is 60 mg/kg/day	W&P: Hepatotoxicity, birth defects, pancreatitis, suicidal behavior or ideation	BW for hepatoxicity, fetal risk and pancreatitis (including fatal hemorrhagic cases)
Prolixin (Fluphenazine) 1960	Psychotic disorders	Oral- 1 -10 mg given at 6 to 8-hour intervals; up to 40 mg	Warnings- TD, NMS	BW for increased mortality in elderly patients with dementia-related psychosis
Haldol (Haloperidol) 1967	Schizophrenia	Oral- Moderate symptomology: 0.5 to 2 mg orally 2 to 3 times a day Severe symptomology: 3 to 5 mg orally 2 to 3 times a day Initial doses of up to 100 mg/day have been necessary in some severely resistant cases. IM- 2 to 5 mg IM every 4 to 8 hours; max 20 mg/day	Warnings- Sudden death, QT-prolongation, and Torsades de Points; tardive dyskinesia; NMS	BW for increased mortality in elderly patients with dementia-related psychosis
Fanapt (Iloperidone) 2009	Schizophrenia	12 to 24 mg/day administered twice daily	W&P: QT prolongation, NMS, Metabolic changes including hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain	BW for increased mortality in elderly patients with dementia-related psychosis

Lamictal (Lamotrigine) 1994	Bipolar disorder (maintenance)	Start at a low dose 25 mg every other day to 50 mg daily. Target dose is 100 to 400 mg depending on concomitant medications	W&P: Hemophagocytic lymphohistiocytosis, fatal or life-threatening hypersensitivity reaction Limitations of Use: Treatment of acute manic or mixed episodes is not recommended.	BW for life-threatening serious rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis, and/or rash-related death
Eskalith (Lithium) 1970	Bipolar disorder (acute manic and mixed episodes as well as maintenance)	Recommended starting dosage for adults Tablets or Capsules: 300 mg, three times daily, or Oral Solution: 8mEq lithium (5 mL) three times daily Maintenance dose based on lithium serum levels	W&P: Lithium-induced polyuria, hyponatremia, lithium-induced chronic kidney disease	BW for lithium toxicity and the need to be close to facilities for prompt and accurate serum lithium determinations
Loxitane (Loxapine) 1975	Schizophrenia	Oral: Initial dosage of 10 mg twice daily but up to 50 mg daily. Usual therapeutic and maintenance range is 60 mg to 100 mg daily. Higher than 250 mg not recommended	Warnings: TD, NMS, falls, leukopenia, neutropenia and agranulocytosis	BW for increased mortality in elderly patients with dementia-related psychosis
Adasuve (Loxapine) 2012	Acute treatment of agitation associated with schizophrenia or bipolar I disorder	Inhaled: 10 mg as a single dose. No more than 1 dose per 24-hour period	W&P: NMS, hypotension and syncope, seizure, cognitive and motor impairment, cerebrovascular adverse reactions (CAR)	BW and REMS for bronchospasm BW for bronchospasm and increased mortality in elderly patients with dementia-related psychosis
Latuda (Lurasidone) 2010	Schizophrenia Bipolar disorder (depressive episode)	Schizophrenia- initial 40 mg/day and recommended dose 40 to 160 mg/day Bipolar Depression- initial 20 mg/day and recommended dose 20 to 120 mg/day	W&P: CAR, NMS, TD, metabolic changes including hyperglycemia, dyslipidemia, and weight gain	BW for increased mortality in elderly patients with dementia-related psychosis and increased risk of suicidal thoughts and behaviors in pediatric and young adult patients
Moban (Molindone) 1974	Schizophrenia	Starting dose- 50 to 75 mg/day Maintenance- Mild symptoms 5 to 15 mg 3-4 x/day; Moderate symptoms 10 to 25 mg 3-4 x/day; Severe symptoms 225 mg/day	Warnings: TD, falls, NMS, leukopenia, neutropenia and agranulocytosis	BW for increased mortality in elderly patients with dementia-related psychosis

Olanzapine Oral- 1996 IM- 2009	Schizophrenia Bipolar disorder (manic and mixed episodes and maintenance)	Oral- 2.5 to 15 mg once daily depending on indication IM- 5 to 10 mg max 3 doses 2-4 hours apart	W&P Oral- Suicide, NMS, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), metabolic changes including hyperglycemia, dyslipidemia, and weight gain, TD IM- Suicide, NMS, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), metabolic changes including hyperglycemia, dyslipidemia, and weight gain, TD	Oral- W&P metabolic changes including hyperglycemia, dyslipidemia, and weight gain IM- BW and REMS for Post-injection delirium/sedation syndrome (PDSS) Both- BW for increased mortality in elderly patients with dementia-related psychosis
Symbyax (Olanzapine/ Fluoxetine) 2003	Bipolar disorder (depressive episode)	Starting dose- 6 mg/25 mg, once daily in the evening; adult maximum Dose- 12 mg/50 mg once daily	W&P: NMS, DRESS, metabolic changes including hyperglycemia, dyslipidemia, and weight gain, serotonin syndrome	BW for increased risk of suicidal thinking and behavior in children, adolescents, and young adults; increased mortality in elderly patients with dementia-related psychosis
Invega (Paliperidone) 2006	Schizophrenia and schizoaffective disorder	Starting dose- 6 mg/day; recommended dose 3 to 12 mg/day; maximum dose 12 mg/day	W&P CAR, NMS, QT prolongation, TD, metabolic changes including hyperglycemia, dyslipidemia, and weight gain	BW for increased mortality in elderly patients with dementia-related psychosis
Trilafon (Perphenazine) 1957	Schizophrenia	Moderately disturbed non-hospitalized patients with schizophrenia starting dose- 4 to 8 mg three times daily; reduce as soon as possible to minimum effective dosage. Hospitalized patients with schizophrenia starting dose- 8 to 16 mg 2 -4 times daily; avoid dosages in excess of 64 mg daily.	W&P: NMS, falls, leukopenia, neutropenia and agranulocytosis	BW for increased mortality in elderly patients with dementia-related psychosis

Compazine (Prochlorperazine) 1956	Schizophrenia	IM- 10 to 20 mg, if necessary, repeat the initial dose every 2-4 hours up to every hour Oral- after control with IM is achieved, switch to oral at the same dosage level or higher	TD, NMS, falls, leukopenia, neutropenia and agranulocytosis	BW for increased mortality in elderly patients with dementia-related psychosis
Seroquel (Quetiapine) 1997	Schizophrenia Bipolar disorder (manic, mixed, and depressive episodes and maintenance)	Schizophrenia- initial 25 mg twice daily increased to 150 to 750 mg/day; maximum dose 750 mg/day Bipolar Mania- initial 50 mg twice daily increased to 400 to 800 mg/day; maximum dose 800 mg/day Bipolar Depression- initial 50 mg once daily at bedtime increased to 300 mg/day; maximum dose 300 mg/day	W&P: CAR, NMS, metabolic changes including hyperglycemia, dyslipidemia, and weight gain, TD	BW for increased risk of suicidal thinking and behavior in children, adolescents, and young adults; increased mortality in elderly patients with dementia-related psychosis
Risperdal (Risperidone) 1993	Schizophrenia Bipolar disorder (acute manic and mixed episodes)	Schizophrenia- initial 2 mg/day with an effective dose range of 4 to 16 mg/day Bipolar mania- initial 2 to 3 mg/day with an effective dose range of 1 to 6 mg/day	W&P: NMS, TD, metabolic changes including hyperglycemia, dyslipidemia, and weight gain.	BW for increased mortality in elderly patients with dementia-related psychosis
Mellaril (Thioridazine) 1962	Schizophrenia	Initial dose- 50 to 100 mg three times daily, with a gradual increment to a maximum of 800 mg daily if necessary.	Warnings: TD, Pregnancy (nonteratogenic effects), NMS, falls	BW for QT prolongation and increased mortality in elderly patients with dementia-related psychosis

Navane (Thiothixene) 1967	Schizophrenia	In milder conditions- initial dose of 2 mg three times daily is recommended. If indicated, a subsequent increase to 15 mg/day total daily dose In more severe conditions- initial dose of 5 mg twice daily The usual optimal dose is 20 mg to 30 mg daily. If indicated, an increase to 60 mg/day total daily dose is often effective. Exceeding a total daily dose of 60 mg rarely increases the beneficial response.	Warnings: TD, Pregnancy (nonteratogenic effects), NMS, leukopenia, neutropenia and agranulocytosis	BW for increased mortality in elderly patients with dementia-related psychosis
Stelazine (Trifluoperazine) 1959	Schizophrenia	Initial- 2 mg to 5 mg twice daily with optimum response on 15 mg or 20 mg daily, although a few may require 40 mg a day or more.	Warnings: TD, NMS, Pregnancy (nonteratogenic effects), leukopenia, neutropenia and agranulocytosis	BW for increased mortality in elderly patients with dementia-related psychosis

Geodon (Ziprasidone) 2001	Schizophrenia Bipolar disorder (manic and mixed episodes and maintenance)	Oral- Schizophrenia: Initiate at 20 mg twice daily. Daily dosage may be adjusted up to 80 mg twice daily. Safety and efficacy have been demonstrated in doses up to 100 mg twice daily. Acute treatment of manic/mixed episodes of bipolar I disorder- Initiate at 40 mg twice daily. Increase to 60 mg or 80 mg twice daily on day 2 of treatment within the range of 40-80 mg twice daily. Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate: Continue treatment at the same dose on which the patient was initially stabilized, within the range of 40-80 mg twice daily. IM- Acute treatment of agitation associated with schizophrenia: 10 mg-20 mg up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every 2 hours. Doses of 20 mg may be administered every 4 hours.	W&P: CAR, QT prolongation, NMS, severe cutaneous Adverse Reasons, TD, metabolic changes including hyperglycemia, dyslipidemia, and weight gain.	BW for increased mortality in elderly patients with dementia-related psychosis

10.2 REFERENCES

[1] Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* 2017 Sep 16;390(10100):1211-1259.

[2] McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol Rev.* 2008;30:67-76

[3] Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. *PLoS Med.* 2005 May;2(5):e141.

[4] Carpenter WT Jr, Strauss JS, Bartko JJ. The diagnosis and understanding of schizophrenia. Part I. Use of signs and symptoms for the identification of schizophrenic patients. Schizophr Bull. 1974;(11):37-49.

[5] Bartko JJ, Strauss JS, Carpenter WT Jr. The diagnosis and understanding of schizophrenia. Part II. Expanded perspectives for describing and comparing schizophrenic patients. Schizophr Bull. 1974;(11):50-60.

[6] Strauss JS, Carpenter WT Jr, Bartko JJ. The diagnosis and understanding of schizophrenia. Part III. Speculations on the processes that underlie schizophrenic symptoms and signs. Schizophr Bull. 1974;(11):61-69.

[7] Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. Am Heart J. 2005;150(6):1115-1121.

[8] Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia: a reexamination. *Arch Gen Psychiatry.* 2005 Mar;62(3):247-53.

[9] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington, VA 2013.

[10] Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication [published correction appears in Arch Gen Psychiatry. 2007 Sep;64(9):1039]. Arch Gen Psychiatry. 2007;64(5):543-552.

[11] Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication [published correction appears in Arch Gen Psychiatry. 2005 Jul;62(7):768. Merikangas, Kathleen R [added]]. Arch Gen Psychiatry. 2005;62(6):593-602.

[12] Hawton K, van Heeringen K. Suicide. Lancet. 2009;373(9672):1372-1381.

[13] Harris EC, Barraclough B. Suicide as an outcome for mental disorders. A meta-analysis. Br J Psychiatry. 1997;170:205-228.

[14] Cloutier M, Greene M, Guerin A, Touya M, Wu E. The economic burden of bipolar I disorder in the United States in 2015. J Affect Disord. 2018;226:45-51.

[15] Lehman, A.F., et al., Practice guidelines for the treatment of patients with schizophrenia. American Journal of Psychiatry, 2004. 161(2 SUPPL).

[16] Rabiner CJ, Wegner JT, Kane JM: Outcome study of first-episode psychosis. I: relapse rates after 1 year. Am J Psychiatry 1986; 143:1155–1158

[17] Leucht S, Barnes TR, Kissling W, Engel RR, Correll C, Kane JM: Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. Am J Psychiatry 2003; 160:1209–1222.

[18] Hirschfeld, R.M., Guideline watch: Practice guideline for the treatment of patients with bipolar disorder, 2nd edition. 2011: American Psych Pub.

[19] Lieberman JA, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209-23.

[20] Alkermes Inc. Summary of Clinical Safety for Lybalvi, November 15, 2019.

[21] Birgenheir DG, et al. Pain conditions among veterans with schizophrenia or bipolar disorder. Gen Hosp Psychiatry. 2013;35(5):480-4.

[22] Owen-Smith A, et al. Chronic pain diagnoses and opioid dispensings among insured individuals with serious mental illness. BMC Psychiatry. 2020;20(1):40.

[23] Substance Abuse and Mental Health Services Administration. (2019). Key substance use and mental health indicators in the United States. Results from the 2018 National Survey on Drug Use and Health (HHS Publication No. PEP19-5068, NSDUH series H-54). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data.

[24] Mallama C, Bak D. Division of Epidemiology. Epidemiology Review for Lybalvi (olanzapine/samidorphan) NDA 213378, November 12, 2020.

[25] Webster MP, Mistry K, Hampp C. Office of Surveillance and Epidemiology Review. Concomitant use of Contrave with an opioid or another bupropion product.

[26] Ninh A, Kim S, Goldberg A. Perioperative Pain Management of a Patient Taking Naltrexone HCl/Bupropion HCl (Contrave): A Case Report. A A Case Rep. 2017 Oct 15;9(8):224-226.

[27] Lopez A, Division of Pharmacovigilance. Concomitant use of Contrave with an opioid product and relevance to Lybalvi, September 24, 2020.

[28] Alkermes Inc. Proposed Prescribing Information for Lybalvi, last updated November 5, 2019.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LEAH M HART
11/13/2020 04:12:34 PM

CAROLYN N TIEU
11/13/2020 04:14:13 PM

DORIS A AUTH on behalf of CYNTHIA L LACIVITA
11/13/2020 04:33:03 PM