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December 20, 2013

OSU College of Pharmacy - Drug Use Research & Management
DHS Division of Medical Assistance Programs
500 Summer Street NE, E35
Salem, OR 97301-1079

Dear OSU College of Pharmacy:

Thank you for your interest in Latuda® (lurasidone HCl) tablets. I'm responding to your request for public comment on the draft documents for the January 30, 2014 Pharmacy and Therapeutics Committee meeting, forwarded by your Account Director, Jeana Colabianchi.

The enclosed information is supplied as a professional courtesy in response to your inquiry. It is intended to provide pertinent data that will assist you in forming your own conclusions and making your own decisions. This information is not intended to advocate any indication, dosage, or other claim that is not covered in the enclosed package insert.

Should you have any questions or need additional information, please contact us directly at 1-800-739-0565 or visit our Medical Information website at www.SunovionMedical.com.

Thank you again for your interest in Latuda.

Sincerely,

Tanya Basu, PharmD, JD, Rph
Manager, Medical Information

CC: Andrei Pikalov, MD, PhD
Executive Director, CNS Clinical Development & Medical Affairs
Enclosure: Package Insert-Latuda® (lurasidone HCl) tablets

2013-008439

Latuda® (lurasidone HCl) – Public Comment on the OSU Class Update: Second Generation Antipsychotics

In response to a request for comment on the recommendations put forth by the OSU College of Pharmacy – Drug Use and Research Management Programs, please find the following information. The studies referenced in the document are being attached for your review.

For U.S. Healthcare Professional Use Only. This information is provided as a professional courtesy in response to your unsolicited request for information and may contain information that is not part of the FDA approved labeling. It is intended to provide pertinent data that will assist you in forming your own conclusions and making your own decisions. This information is not intended to advocate any indication, dosage, or other use that is not covered in the Full Prescribing Information. Please see the enclosed Full Prescribing Information for important safety information, including ***Boxed Warnings****.*[1] *Do Not Copy or Distribute. For Informational Purposes Only.*

Bipolar Depression

Lurasidone is the only atypical antipsychotic approved for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression), both as monotherapy and as adjunctive therapy with lithium or valproate

Two 6-week, double-blind, placebo-controlled, fixed-flexible dose, multicenter studies demonstrated the safety and efficacy of lurasidone treatment, either as monotherapy or as adjunctive to lithium or valproate, with stable therapeutic levels, as compared to placebo in adult depressed bipolar I patients.

Both these studies were recently published in the *American Journal of Psychiatry.*

> Loebel A, Cucchiaro J, Silva R, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study [published online ahead of print October 30, 2013]. *Am J Psychiatry*. http://dx.doi.org/10.1176/appi.ajp.2013.1307085.
>
> Loebel A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study [published online ahead of print October 30, 2013]. *Am J Psychiatry*. http://dx.doi.org/10.1176/appi.ajp.2013.13070984.

Comparative Evidence in Schizophrenia

The OSU and DERP review omits the relapse and rehospitalization information from **a Phase III, randomized, double-blind, controlled clinical trial which included an active comparator (quetiapine XR).** This study showed that probability of relapse at Month 12 endpoint were 23.7% for lurasidone and 33.6% for the active comparator, quetiapine-XR (utilizing a Cox proportional hazards model, assessing non-inferiority of lurasidone compared to quetiapine XR for risk for relapse) . The probability of hospitalization at 12 months was lower for the lurasidone group compared with the quetiapine-XR group (9.8% vs. 23.1%; log-rank p = 0.049). A significantly higher proportion of lurasidone subjects achieved remission at study endpoint compared with the quetiapine-XR group (61.9% vs. 46.3%; p = 0.043). Discontinuation due to insufficient clinical response was lower in the lurasidone group compared with the quetiapine-XR group (9.3% vs. 21.2%). Mean observed weight change in patients who completed 12 months of treatment was 0.7 kg for lurasidone and 1.2 kg for quetiapine XR. A ≥7% weight gain was observed at Month 12

endpoint in 11.5% of lurasidone-treated patients compared to 15.2% of quetiapine XR treated patients. The reference is provided below:

> Loebel A, Cucchiaro J, Xu J, Sarma K, Pikalov A, Kane JM. Effectiveness of lurasidone vs. quetiapine XR for relapse prevention in schizophrenia: A 12-month, double-blind, noninferiority study. *Schizophr Res.* 2013;147:95-102.

Effect on Daytime Sleepiness

Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) in a 6-week, double-blind trial with fixed doses of lurasidone 80 mg/day (n=125), lurasidone 160 mg/day (n=121), quetiapine XR 600 mg/day (n=119), or placebo (n=121). At week 6 endpoint, daytime sleepiness improved in the lurasidone and placebo-treated groups but worsened in the quetiapine XR treatment group when compared to placebo (p=0.001) and to either dose of lurasidone (both p<0.01).

> Loebel AD, Siu CO. Cucchiaro JB, PIkalov AA, Harvey PD. Daytime sleepiness associated with lurasidone and quetiapine XR: results from a randomized double-blind, placebo-controlled trial in patients with schizophrenia. [published online ahead of print]. *CNS Spectrums.* doi:10.1017/S1092852913000904.

Numbers Needed to Treat (NNT)/Numbers Needed to Harm Analyses

A recently published article provides the NNT and NNH analysis for lurasidone in the treatment of bipolar depression. The analysis was done based on the two bipolar depression studies described above. The analysis showed that NNT versus placebo for response was 5 for lurasidone monotherapy (both dose ranges) and 7 for adjunctive therapy. NNT versus placebo for remission for lurasidone monotherapy was 6 for 20-60 mg/d and 7 for 80-120 mg/d and 7 for adjunctive lurasidone.

> Citrome L, Ketter TA, Cucchiaro J, Loebel A. Clinical assessment of lurasidone benefit and risk in the treatment of bipolar I depression using number needed to treat, number needed to harm, and likelihood to be helped or harmed. [published online ahead of print October 28, 2013]. *Affect Disord.* doi: 10.1016/j.jad.2013.10.040.

The NNT/NNH analysis for schizophrenia was published in 2012 and is referenced below.

> Citrome L. Lurasidone for the acute treatment of adults with schizophrenia: what is the number needed to treat, number needed to harm, and likelihood to be helped or harmed? *Clin Schizophr & Relat Psychoses*. 2012;6(2):76-85.

<u>Switch Study</u>

A 6-week, open-label trial assessed the completion rate and rate of treatment failure for clinically stable, but symptomatic patients with schizophrenia/schizoaffective disorder switched from other antipsychotics to lurasidone.

There were no clinically significant differences in time to treatment failure (defined as insufficient clinical response, exacerbation of underlying disease, or discontinuation due to an adverse event), or all cause discontinuation, irrespective whether patients started on lurasidone doses of 40 or 80 mg/day, or started at 40 mg/day in Week 1 and escalated to 80 mg/day for Week 2.

McEvoy JP, Citrome L, Hernandez D, et al. Effectiveness of lurasidone in patients with schizophrenia or schizoaffective disorder switched from other antipsychotics: A randomized, 6-week, open-label study. *J Clin Psychiatry*. 2013;74(2):170-179.

A 6-month open-label extension of the switch study above has recently been published:

Citrome L, Weiden PJ, McEvoy JP, et al. Effectiveness of lurasidone in schizophrenia or schizoaffective patients switched from other antipsychotics: a 6-month, open-label, extension study. [published online ahead of print December 2013]. *CNS Spectrums.* doi:10.1017/S109285291300093X.

Schizophrenia

Lurasidone is indicated for the treatment of schizophrenia (efficacy established in five 6-week controlled studies in adults).

All of the five studies have been published in peer-reviewed journals. Two of the studies have an active control arm to assess assay sensitivity (olanzapine and quetiapine). These studies have been provided previously but are referenced again below.

Loebel A, Cucchiaro J, Sarma K, et al. Efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia: A randomized, double-blind, placebo- and active controlled trial. *Schizophr Res*. 2013;145(1-3):101-109.

Meltzer HY, Cucchiaro J, Silva R, et al. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study. *Am J Psychiatry*. 2011; 168:957-67.

Nakamura M, Ogasa M, Guarino J, et al. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2009; 70(6):829-36.

Nasrallah HA, Silva R, Phillips D, et al. Lurasidone for the treatment of acutely psychotic patients with schizophrenia: A 6-week, randomized, placebo-controlled study. [published online ahead of print]. *J Psychiatr Res*. 2013; 47(5):670-677.

Ogasa M, Kimura T, Nakamura M, Guarino J. Lurasidone in the treatment of schizophrenia: a 6-week, placebo-controlled study. *Psychopharmacol*. 2013;225:519-530.

INDICATIONS AND USAGE[1]

- LATUDA is indicated for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with either lithium or valproate
- LATUDA is indicated for the treatment of patients with schizophrenia.

The efficacy of LATUDA as monotherapy and adjunctive therapy with lithium or valproate for the treatment of bipolar depression, were each established in a 6-week controlled study of adult patients with bipolar depression.

The efficacy of LATUDA in schizophrenia was established in five 6-week controlled studies of adult patients with schizophrenia.

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for

extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. The efficacy of LATUDA in the treatment of mania associated with bipolar disorder has not been established.

BOXED WARNINGS

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; AND SUICIDAL THOUGHTS AND BEHAVIORS

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **LATUDA is not approved for use in patients with dementia-related psychosis.**
- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants.**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors.**

***(See Warnings and Precautions Section 5.1 and 5.2 of the enclosed full Prescribing Information)*.**

DOSAGE AND ADMINISTRATION[1]

LATUDA should be taken with food (at least 350 calories).

Schizophrenia: The recommended starting dose of LATUDA is 40 mg once daily. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 40 mg/day to 160 mg/day. The maximum recommended dose is 160 mg/day.

Bipolar Depression: The recommended starting dose of LATUDA is 20 mg given once daily as monotherapy or as adjunctive therapy with lithium or valproate. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 20 mg/day to 120 mg/day as monotherapy or as adjunctive therapy with lithium or valproate. The maximum recommended dose, as monotherapy or as adjunctive therapy with lithium or valproate, is 120 mg/day. In the monotherapy study, the higher dose range (80 mg to 120 mg per day) did not provide additional efficacy on average, compared to the lower dose range (20 to 60 mg per day).

Dose Adjustments

Renal Impairment: Dose adjustment is recommended in moderate (creatinine clearance: 30 to <50 mL/min) and severe renal impairment (creatinine clearance <30 mL/min) patients. The recommended starting dose is 20 mg/day. The dose in these patients should not exceed 80 mg/day.

Hepatic Impairment: Dose adjustment is recommended in moderate (Child-Pugh Score = 7 to 9) and severe hepatic impairment (Child-Pugh Score = 10 to 15) patients. The recommended starting dose is 20 mg/day. The dose in moderate hepatic impairment patients should not exceed 80 mg/day and the dose in severe hepatic impairment patients should not exceed 40 mg/day.

Concomitant Use with CYP3A4 Inhibitors: LATUDA should not be used concomitantly with a strong CYP3A4 inhibitor (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.). If LATUDA is being prescribed and a moderate CYP3A4 inhibitor (e.g., diltiazem, atazanavir, erythromycin, fluconazole, verapamil, etc.) is added to the therapy, the LATUDA dose should be reduced to half of the original dose level. Similarly, if a moderate CYP3A4 inhibitor is being prescribed and LATUDA is added to the therapy, the recommended starting dose of LATUDA is 20 mg per day, and the maximum recommended dose of LATUDA is 80 mg per day. Grapefruit and grapefruit juice should be avoided in patients taking LATUDA.

Concomitant Use with CYP3A4 Inducers: LATUDA should not be used concomitantly with a strong CYP3A4 inducer (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.). If LATUDA is used concomitantly with a moderate CYP3A4 inducer, it may be necessary to increase the LATUDA dose after chronic treatment (7 days or more) with the CYP3A4 inducer.

REFERENCE

1. Latuda® (lurasidone HCl) tablets [package insert]. Marlborough, Mass: Sunovion Pharmaceuticals Inc.

Caring Ambassadors Program
Lorren Sandt, Executive Director
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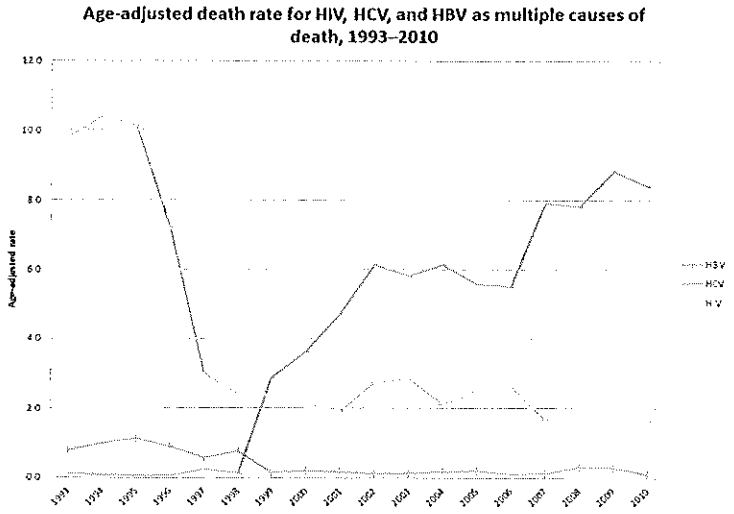
Public Comment
Hepatitis C PDL Class Review

OSU Drug Use Research and Management Program
January 30, 2014

I. INTRODUCTION

The Caring Ambassadors Program is a national, nonprofit, advocacy organization based in Oregon City, Oregon. We respectfully submit our written comment on the Hepatitis C Class Review and suggested revision to the current Hepatitis C PDL class to include all Simeprevir and Sofosbuvir for treatment of Chronic Hepatitis C (CHC) Virus.

Hepatitis C is the **most common**, chronic, blood-borne viral infection in the United States, yet it remains an unrecognized threat in the minds of many Americans. While an estimated 1 million Americans have been infected with the human immunodeficiency virus (HIV)[i], at least 2.7 to 3.9 million Americans [ii] are chronically infected with the hepatitis C virus including an estimated 60,000 Oregonians. The Centers for Disease Control and Prevention (CDC) state that approximately 17,000 new cases of HCV infection occur annually. [iii] Each year deaths due to hepatitis C surpass deaths due to HIV in the US. [iv] In Oregon, we surpassed HIV deaths in 1998. Since 1999, Oregon has seen a tripling of the death rate from HCV. [v]



Hepatitis C is an insidious and often silent disease for many years. The early quiescent nature of chronic hepatitis C is one of the most fundamental reasons it poses such a perilous public health threat. Significant numbers of people currently infected with HCV are unaware of their infection and are likely to remain so for many years until the complications of chronic liver disease develop. And in the interim, tens of thousands of infected Oregonians run the risk of unwittingly infecting countless other citizens with this potentially life-threatening virus.

II. HEPATITIS C TREATMENT

The development of *direct acting antivirals (DAA's)* changed the landscape for genotype 1 patients. In 2011, the first two oral drugs, *protease inhibitors*, Vertex's telaprevir (Incivek) and Merck's boceprevir (Victrelis) were approved by the FDA in 2011 for people with genotype 1. In clinical trials, both agents used in conjunction with pegylated interferon and ribavirin resulted in substantially higher SVR rates [vi-viii] . However, the management and side effects from these combinations have proved to be too much for many patients and therefore many specialists have stopped prescribing these regimens.

The FDA approval of the second generation Protease inhibitor, Simeprevir, and Sofosbuvir a prodrug of a nucleotide analogue inhibitor of the HCV NS5B RNA-dependent RNA polymerase, is a new paradigm shift for HCV treatment.[ix,x] **The prospect of interferon free regimens is exciting and will allow all people with HCV access to therapy that is less toxic and highly effective.**

To provide healthcare professionals with timely guidance as new therapies are available and integrated into HCV regimens, the Infectious Diseases Society of America (IDSA) and American Association for the Study of Liver Diseases (AASLD) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management.[xi] The AASLD/IDSA hepatitis C Guidance is supported by the membership-based societies and not by pharmaceutical companies or other commercial interests. **Some of your recommendations are not in line with experts in the field. Caring Ambassadors strongly recommends you follow the AASLD/IDSA guidelines. They can easily be found on the web and should be followed by any qualified provider in the Oregon health plan system. http://www.hcvguidelines.org/full-report/introduction**

Patients and doctors treating hepatitis C patients of all genotypes should retain the professional freedom to choose which combination of drugs are most likely to be effective when curative treatment for hepatitis C is deemed appropriate.

III. CONCLUSIONS

From both a public health perspective and for the sake of those afflicted with chronic hepatitis C, it is imperative that health care providers be afforded the freedom to choose from a complete and evolving armament of medications to combat the HCV epidemic facing the citizens of Oregon. **CAP strongly supports doctors treating hepatitis C patients of all genotypes should retain the professional freedom to choose which combination of drugs are most likely to be**

effective when curative treatment for hepatitis C is deemed appropriate. Limiting the choice of drugs available to physicians treating hepatitis C patients has the scary potential to **increase avoidable deaths** due to hepatitis C and **promote drug resistance in the virus** itself, making it more difficult to control the infection in the population. We should not tie the hands of our physicians, those on the front lines of fighting the hepatitis C crisis in Oregon, by dictating decisions that only they have the knowledge, skills, and abilities to make. Medicine is both art and science; it cannot be effectively practiced by prescriptive bureaucracy.

Thank you for your time and consideration.

Lorren Sandt
Executive Director
Caring Ambassadors Program

REFERENCES

i. HIV in the United States: An Overview. http://www.cdc.gov/hiv/topics/surveillance/resources/factsheets/incidence-overview.htm Last accessed January 25, 2112

ii. Armstrong GL et al. The prevalence of Hepatitis C virus infection in the United States, 1999 through 2002. Ann Int Med 2006;144:705-14.

iii. Incidence estimates for Hepatitis C are derived by adjusting rates from the Sentinel Counties Study of Viral Hepatitis (1982–2006) and Emerging Infection Program (2007) for underreporting and asymptomatic infection. http://www.cdc.gov/hepatitis/HCV/StatisticsHCV.htm Last accessed January 25, 2012.

iv. Holmberg SD, et al "The growing burden of mortality associated with viral hepatitis in the United States, 1999 - 2007" *Hepatology* 2011; 54(4): Abstract 243.

v. Data presented by Judith Leahy, Adult Viral Hepatitis Prevention Coordinator, Oregon Health Authority. Region X HIV and Viral Hepatitis Strategy Meeting. May 9, 2012 Seattle, WA HIV and Viral Hepatitis Strategy Meeting. May 9, 2012 Seattle, WA

vi. Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. Lancet. Aug 28 2010;376(9742):705-716.

vii. Pawlotsky JM. The results of Phase III clinical trials with telaprevir and boceprevir presented at the Liver Meeting 2010: a new standard of care for hepatitis C virus genotype 1 infection, but with issues still pending. Gastroenterology. Mar 2011;140(3):746-754.

viii. Poordad F, McCone J, Jr., Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. Mar 31 2011;364(13):1195-1206.

ix. The U.S. Food and Drug Administration today approved Olysio (simeprevir), a new therapy to treat chronic hepatitis C virus infection. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm376449.htm last accessed 1/30/14

x. Approval of Sovaldi (sofosbuvir) tablets for the treatment of chronic hepatitis C. http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/ucm377920.htm last accessed 1/30/14

xi. Recommendations for Testing, Managing, and Treating Hepatitis C. http://www.hcvguidelines.org/full-report/introduction, last accessed 1/30/14