

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC.,  Plaintiff,  v.  AVADEL CNS PHARMACEUTICALS, LLC,  Defendant.	C.A. No. 21-691-GBW  [REDACTED]  PUBLIC - REDACTED VERSION Original Filing Date: June 17, 2025 Redacted Filing Date: July 9, 2025
JAZZ PHARMACEUTICALS, INC., et al.,  Plaintiffs,  v.  AVADEL CNS PHARMACEUTICALS, LLC,  Defendant.	C.A. No. 21-1138-GBW  [REDACTED]  PUBLIC - REDACTED VERSION Original Filing Date: June 17, 2025 Redacted Filing Date: July 9, 2025
JAZZ PHARMACEUTICALS, INC., et al.,  Plaintiffs,  v.  AVADEL CNS PHARMACEUTICALS, LLC,  Defendant.	C.A. No. 21-1594-GBW  [REDACTED]  PUBLIC - REDACTED VERSION Original Filing Date: June 17, 2025 Redacted Filing Date: July 9, 2025

**DECLARATION OF RICHARD K. BOGAN IN SUPPORT OF PLAINTIFFS’  
RENEWED MOTION FOR A PERMANENT INJUNCTION**

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I, Richard K. Bogan, MD, FCCP, FAASM, submit this declaration on behalf of Jazz Pharmaceuticals, Inc. and Jazz Pharmaceuticals Ireland Limited (together, “Jazz”).

## **I. EXPERT QUALIFICATIONS**

1. I am an expert in the field of sleep medicine and have a recognized reputation for patient care in the diagnosis and treatment of sleep disorders. With over 35 years of experience in the sleep medicine field, I built the largest sleep company in the nation. I have also helped numerous board-certified pulmonologists and neurologists establish sleep disorder laboratories in local community hospitals and provided them with training, peer review, and support. I am American Board-certified in internal medicine, pulmonary disease, and sleep medicine. I am also an Associate Clinical Professor at the University of South Carolina Medical School, Columbia, South Carolina. I have nearly 50 years’ experience practicing medicine and have been involved in clinical trial investigations for more than 30 years, including for both Jazz and Avadel CNS Pharmaceuticals, LLC (“Avadel”).

2. I earned a Bachelor of Science degree from Wofford College, Spartanburg, South Carolina, in 1966. In 1970, I was awarded my Medical Degree from the Medical University of South Carolina, Charleston, South Carolina. From 1970-1971, I was an Intern at the University of Alabama Hospital and Clinics, Birmingham, Alabama. In 1974, I became a Resident in internal medicine at the University of Alabama Hospital and Clinics, and held that position until I was promoted to Chief Resident in 1975. In 1976, I earned a fellowship in the University of Alabama School of Medicine’s Pulmonary Division, Department of Medicine, and held that position until 1978. I spent the brief absence from my educational background, from 1972-1974, serving as Lt. Commander in the United States Navy.

3. I am currently the owner of Bogan Sleep Consultants, LLC and the President of Bogan Consulting Services, PA. I am also Associate Clinical Professor at the Medical University of South Carolina. From 1999 to 2020, I was the Chief Medical Officer of SleepMed, Inc.

4. I have been licensed to practice medicine since 1971. I am licensed in South Carolina. In 1975, I became American Board-certified in Internal Medicine. In 1978, I gained my certification from the American Board of Pulmonary Diseases. In 1989, I became one of the first physicians in the nation to become American Board-certified in Sleep Medicine. In 2009, I obtained a Sleep Medicine Certificate from the American Board of Medicine.

5. Since 1980, I have devoted my practice of medicine to the diagnosis and treatment of various sleep disorders. From 1978-1994, I also practiced in the field of pulmonary and critical care medicine. In 1994, I founded Sleep Disorder Centers of America and served as its President until 1999. In 1999, Sleep Disorder Centers of America merged with DigiTrace Care Services, Inc. to form SleepMed, Inc. Upon merger, I was named Chairman, Chief Medical Officer, a position I held until a merger and subsequent sale. SleepMed, Inc. merged with Watermark Inc. in April 2013 to establish the largest sleep diagnostic, therapeutic, and research sleep company in the United States. SleepMed, Inc. was acquired by BioSerenity, Inc. in 2020.

6. In addition to practicing medicine, I have also been Principal Investigator on more than 250 clinical trials investigating sleep disorders. I am former Chairman of the National Sleep Foundation 2019-2021 and Director 2011-2021. In the past, I have also been Medical Director for both Premier Health Systems, Inc. and Baptist Physician Partners. I also served on the Board of Directors for Premier Health Systems, Inc., as well as the American Lung Association, South Carolina.

7. Over my career, I have been a member of a number of professional organizations. These organizations include the American Academy of Sleep Medicine, Sleep Research Society, European Sleep Research Society, World Sleep Society, American Medical Association, American College of Chest Physicians, American Thoracic Society, South Carolina Medical Association, and South Carolina Lung Association.

8. I have authored or co-authored more than 160 publications, including approximately 50 peer-reviewed publications and 110 abstracts focused on sleep disorder diagnosis and management, including narcolepsy and idiopathic hypersomnia (“IH”). I have published on behalf of both Jazz and Avadel. I have also been invited to give lectures on several occasions.

9. For a complete list of my professional experience, publications, and invited lectures, please see my curriculum vitae attached hereto as Exhibit A.

10. I am being compensated at my usual rate of \$600/hour in connection with this proceeding. My compensation is not dependent in any way on the outcome of anything related to this declaration.

## **II. MATERIALS CONSIDERED**

11. The materials that I have reviewed in connection with my opinions include the documents cited herein.

12. The opinions presented below are based on my education and experience that I have acquired during the course of my clinical practice treating patients with sleep disorders, as well as the information available to me as of the date of this declaration.

**III. THE FDA APPROVED LABELING WILL INSTRUCT AND ENCOURAGE PRESCRIBERS TO PRESCRIBE LUMRYZ FOR THE INDICATIONS ON THE LABELING**

13. I have been asked to determine whether the inclusion of idiopathic hypersomnia (“IH”) as an indication on the LUMRYZ package insert will instruct or encourage doctors, pharmacists, or other healthcare professionals to prescribe LUMRYZ to treat patients with IH.

14. For the reasons set forth below, it is my opinion that the package insert for LUMRYZ will instruct or encourage doctors, pharmacists, or other healthcare professionals to prescribe LUMRYZ for the treatment of any and all indications listed in the package insert.

15. As to IH in particular, it is my opinion that should the LUMRYZ package insert be modified to include an indication for IH, doctors, pharmacists, or other healthcare professionals will be instructed and encouraged to prescribe LUMRYZ to treat patients with IH.

16. I understand that Avadel stipulated to infringement of claim 24 of Jazz’s ’782 patent, and that the Court granted Jazz’s motion for judgment as a matter of law that Avadel infringed claim 24 of the ’782 patent. I also understand that the jury determined claim 24 to be not invalid.

17. I understand from counsel that Avadel is currently enjoined from marketing, making, using, or selling LUMRYZ for the treatment of IH or any other indication not on its label as of March 4, 2024.

18. I understand from counsel that Jazz currently seeks a permanent injunction to enjoin Avadel from requesting FDA approval of LUMRYZ for use in IH until February 19, 2036.

**A. The LUMRYZ Package Insert Instructs and Encourages the Use of LUMRYZ for the Treatment of Patients with Narcolepsy**

19. Avadel’s LUMRYZ is currently indicated “for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.” Ex. B,

Label at 3. It is my opinion that the Indications and Usage section of the LUMRYZ package insert instructs doctors, pharmacists, other healthcare professionals, and/or patients to use LUMRYZ to treat cataplexy and excessive daytime sleepiness in patients diagnosed with narcolepsy.

20. The Dosage and Administration section of the LUMRYZ package insert states that the “recommended starting dosage of LUMRYZ in adults is 4.5 grams (g) once per night administered orally. Increase the dosage by 1.5 g per night at weekly intervals to the recommended dosage range of 6 g to 9 g once per night orally. The dosage may be gradually titrated based on efficacy and tolerability. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.” Ex. B, Label at 3. It is my opinion that the Dosage and Administration section of the LUMRYZ package insert instructs and encourages doctors, pharmacists, other healthcare professionals, and/or patients to dose LUMRYZ using the described dose titration regimen until a dosage of 6 g to 9 g is achieved.

21. The Dosage and Administration section of the LUMRYZ package insert states that “[p]atients who are currently being treated with immediate-release sodium oxybate may be switched to LUMRYZ at the nearest equivalent dosage in grams per night (e.g., 7.5 g sodium oxybate divided into two 3.75 g doses per night to 7.5 g LUMRYZ once per night).” Ex B, Label at 4. It is my opinion that the Dosage and Administration section of the LUMRYZ package insert instructs and encourages doctors, pharmacists, and other healthcare professionals to switch patients being treated with twice-nightly oxybate drug products to LUMRYZ.

22. The Clinical Studies section of the LUMRYZ package insert also instructs and encourages the use of LUMRYZ for the treatment of cataplexy and excessive daytime sleepiness in patients diagnosed with narcolepsy using a dose titration regimen in patients until a dosage of 6 g to 9 g is achieved.

23. In general, the Clinical Studies section of a package insert for a given drug includes a description of the Phase III clinical studies conducted for that drug. The description of each Phase III clinical study includes both an overview of the protocol implemented and the results of the study. Doctors and other healthcare professionals often make prescribing decisions, such as what conditions to treat and in what dosages, based on the information disclosed in this section because this section describes the studies that proved the drug is safe and effective in treating the indication identified on the label.

24. As to LUMRYZ, it is my understanding that doctors, pharmacists, and other healthcare professionals review the Clinical Studies section of the LUMRYZ package insert to make prescribing decisions in treating patients with narcolepsy. Healthcare professionals rely on the results of the clinical studies summarized in the LUMRYZ package insert to determine whether to prescribe LUMRYZ to patients with narcolepsy. The protocol implemented in the clinical trial described in the Clinical Studies section informs doctors, pharmacists, and other healthcare professionals on the dosing and dosing regimen that proved to be safe and effective in treating the indication on the label. Doctors, pharmacists, and healthcare professionals rely on this information to prescribe the appropriate dose and dosing regimen for a given patient.

25. The Clinical Studies section of the LUMRYZ package insert includes clinical trial data establishing the “effectiveness of LUMRYZ for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy,” which was “based on a double-blind, randomized, placebo-controlled, two-arm multi-center study to assess the efficacy and safety of a once nightly administration of LUMRYZ in patients with narcolepsy.” Ex. B, Label at 21.

26. Lumryz’s package insert states that “[t]he mean MWT at baseline was 5 minutes for the LUMRYZ group, and 4.7 minutes for the placebo group. The mean number of cataplexy



attacks per week at baseline was 18.9 in the LUMRYZ group and 19.8 in the placebo group. A statistically significant improvement was seen on the MWT, CGI-I, and mean weekly cataplexy attacks, for the 6 g (Week 3), 7.5 g (Week 8), and 9 g (Week 13) dose of LUMRYZ, compared to the placebo group.” Ex. B, Label at 21. The inclusion of those results in this section informs healthcare professionals that LUMRYZ is effective in treating cataplexy and excessive daytime sleepiness in patients with narcolepsy. These results instruct and encourage doctors, pharmacists, and other healthcare professionals to prescribe LUMRYZ in patients with narcolepsy.

27. The Clinical Studies section also provides the dosing regimen used in the clinical study establishing efficacy of LUMRYZ to treat cataplexy and excessive daytime sleepiness in narcolepsy. For example, the package insert states that “[t]he study was divided into four sequential study periods, and incorporated dose titration to stabilized dose administration of LUMRYZ (4.5 g, 6 g, 7.5 g, and 9 g). There was a three-week screening period, a 13-week treatment period including up-titration over a period of eight weeks, five weeks of stable dosing at 9 g/night, and a one-week follow-up period.” Ex. B, Label at 21.

28. Broadly, the dose titration regimen and final stable dosage implemented in the Phase III clinical study aligns with the dosage recommendations provided in the Dosage and Administration section of the LUMRYZ package insert. Both the dose titration regimen implemented in the Phase III clinical study and the dosage recommendation provided in the Dosage and Administration section include an initial dosage of 4.5 g of LUMRYZ, followed by increased dosages at intervals of 1.5 g. *Compare* Ex. B, Label at 3 *with id.* at 21. Both the dose titration regimen implemented in the Phase III clinical study and the dosage recommendation provided in the Dosage and Administration section also include a final dosage of up to 9 g. *Compare* Ex. B, Label at 3 *with id.* at 21. In addition, the dose titration regimen implemented in

the Phase III clinical study and the dosage recommendation provided in the Dosage and Administration section each call for once nightly administration of LUMRYZ. *Compare* Ex. B, Label at 3 *with id.* at 21. Therefore, it is my opinion that the protocol summarized in the Clinical Studies section of the LUMRYZ package insert instructs and encourages doctors, pharmacists, and other healthcare professionals to prescribe LUMRYZ in patients with narcolepsy in accordance with a dosing regimen similar to that described in the Dosage and Administration section of the LUMRYZ package insert.

**B. If Approved for IH, the LUMRYZ Package Insert Will Instruct and Encourage the Use of LUMRYZ for the Treatment of Patients with IH**

29. Avadel is currently conducting a Phase III clinical study to establish the efficacy of LUMRYZ for the treatment of IH. Specifically, Avadel is conducting a double-blind, placebo-controlled, randomized withdrawal, multicenter study of the efficacy and safety of LUMRYZ in the treatment of IH (“REVITALYZ”). Ex. C, Protocol at 1.

30. I understand from counsel that Avadel intends to rely on the results of REVITALYZ to seek FDA approval of LUMRYZ for IH.

31. I understand from counsel that once approved for IH, the Indications and Usage section of the LUMRYZ package insert must be modified to include IH. I also understand from counsel that once approved for IH, the Dosage and Administration section of the LUMRYZ package insert must include dosage and dosing regimen recommendations for patients with IH.

32. I understand from counsel that once approved for IH, the Clinical Studies section of the LUMRYZ package insert must include a summary of REVITALYZ. This will include an overview of the protocol used in the study and a summary of the clinical trial data. This conforms with my experience in working on clinical studies for medications where, if the FDA approves a

new indication, that indication is added to the label, and a summary of the Phase III clinical data supporting the new indication is added to the label.

33. It is my opinion that once LUMRYZ is approved for IH, and the LUMRYZ package insert includes an IH indication, doctors, pharmacists, and other healthcare professionals will prescribe LUMRYZ to treat patients with IH, and patients will use LUMRYZ for IH, even if Avadel is enjoined from making, using, and selling LUMRYZ for use in IH.

34. It is also my opinion that doctors, pharmacists, and other healthcare professionals will understand that the Phase III clinical study results summarized in the FDA-approved LUMRYZ package insert will support the recommended dosages and dosing regimens provided in the Dosage and Administration section of the LUMRYZ package insert. Therefore, the inclusion of Phase III clinical studies for additional indications of LUMRYZ, such as IH, in the LUMRYZ package insert will instruct and encourage doctors, pharmacists, and other healthcare professionals to prescribe LUMRYZ for that use.

35. As discussed above, doctors, pharmacists, and other healthcare professionals review the Indications and Usage and Dosage and Administration sections of package inserts to determine whether and how to prescribe a given drug. Should the LUMRYZ package insert state that LUMRYZ is indicated for the treatment of patients with IH, doctors, pharmacists, and other healthcare professionals will be instructed and encouraged to prescribe LUMRYZ to patients for the treatment of IH. Similarly, should the LUMRYZ package insert include dosing and dosing regimen recommendations in connection with the treatment of IH, doctors, pharmacists, and other healthcare professionals will be instructed and encouraged to prescribe LUMRYZ to patients for the treatment of IH using the dosing amount and regimen so instructed.

36. In addition, as discussed above, the current LUMRYZ package insert includes a section instructing and encouraging prescribers to switch patients from immediate-release sodium oxybate to LUMRYZ. Ex. B, Label at 4. The language of this section is indication-agnostic. This section of the label will therefore inform prescribers how to switch IH patients from other oxybate products to LUMRYZ. Therefore, once the IH indication is in the LUMRYZ package insert, prescribers will be instructed and encouraged to switch patients from Xywav, the only FDA-approved oxybate drug product indicated for the once-nightly treatment of IH, to LUMRYZ.

37. In addition, it is my opinion that doctors, pharmacists, and other healthcare professionals will prescribe LUMRYZ for IH based on both the REVITALYZ protocol and results as summarized in the LUMRYZ package insert. As discussed above with respect to narcolepsy, doctors and other healthcare professionals will decide whether to prescribe LUMRYZ for use in IH based on the results summarized in the Clinical Studies section of the LUMRYZ package insert. Further, doctors and other healthcare professional will determine which doses and dosing regimen are appropriate for a given patient in the treatment of IH based on the REVITALYZ protocol and results as summarized in the LUMRYZ package insert.

38. The REVITALYZ protocol states that the study will include an open-label dose titration period for ten weeks, a stable dose period for two weeks, and a double-blind randomized withdrawal period for two weeks. Ex. C, Protocol at 4. During the open-label dose titration period, “[s]ubjects not currently taking oxybate therapy should take 4.5 g FT218 nightly for Week 1, then increase to 6 g nightly for Weeks 2 and 3, then increase to 7.5 g nightly for Weeks 4 and 5. After Week 5, subjects can increase to 9 g nightly if clinically indicated or can stay on the 7.5 g dose. An increase to 9 g can be initiated at Weeks 6, 7 or 8. No further dose changes should be made during Weeks 9 and 10.” Ex. C, Protocol at 5.

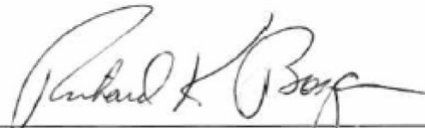
39. During the stable dose period, “[s]ubjects will remain on the stable FT218 dose, unchanged, during this 2-week period. Upon completion of the SD Period, subjects will be assessed for randomization eligibility.” Ex. C, Protocol at 5.

40. During the double-blind randomized withdrawal period, one group of subjects will continue treatment at the stable dose for two weeks and a second group of subjects will initiate a placebo equivalent to the stable dose for two weeks. Ex. C, Protocol at 5-6.

41. The dose titration regimen and final stable dosages being implemented in the REVITALYZ trial are similar to the dosage recommendations provided in the Dosage and Administration section of the LUMRYZ package insert for narcolepsy. Both include an initial once-nightly dosage of 4.5 g, increased dosages at intervals of 1.5 g, and final dosages of up to 9 g. It is therefore my opinion that the recommended dosing and titration regimen for LUMRYZ in the treatment of IH will be similar or identical to the dosage and dosing recommendations provided in the LUMRYZ package insert for narcolepsy. Therefore, it is my opinion that once LUMRYZ is approved for the treatment of IH, the Clinical Studies section of the LUMRYZ package insert will instruct and encourage doctors, pharmacists, and other healthcare professionals to prescribe LUMRYZ to patients with IH in accordance with a dosing regimen similar to that implemented for patients with narcolepsy.

42. In conclusion, it is my opinion that should the LUMRYZ package insert be modified to include an indication for IH, doctors, pharmacists or other healthcare professionals will be instructed and/or encouraged to prescribe LUMRYZ to patients for the treatment of IH in the manner described in the LUMRYZ package insert.

I declare under penalty of perjury that the foregoing is true and correct.

  
Richard K. Bogan, M.D., FCCP

Dated: June 17, 2025

# **EXHIBIT A**

**Richard K. Bogan, MD, FCCP, FAASM**

Bogan Sleep Consultants, LLC

1333 Taylor Street, Suite 6-B

Columbia, SC 29201

Phone : 803-251-3093

Fax : 803-376-1876

Email : [richard.bogan@bogansleep.com](mailto:richard.bogan@bogansleep.com)

**EDUCATION:**

- **Wofford College**, Spartanburg, SC; B.S. (Chemistry), 1966
- **Medical University of South Carolina**, Charleston, SC; M.D. 1970
- **University of Alabama Hospital and Clinics**; Internship – Medicine, Birmingham, AL, 1970-1971
- **University of Alabama Hospital and Clinics**; Residency - Internal Medicine, Birmingham, AL, 1974-1975
- **University of Alabama School of Medicine**; Fellowship - Pulmonary Division, Department of Medicine, 1976-1978

**CREDENTIALS:**

- Certified, American Board of Internal Medicine, 1975
- Certified, American Board of Pulmonary Diseases, 06/1978
- Certified, American Board of Sleep Medicine, 04/1989
- Certified, American Board of Medicine, Sleep, 11/2009
- Certified, American Board of Critical Care, 11/1992 (expired)

**LICENSE NUMBERS:**

- South Carolina: 8796
- NPI 1538347661

**CURRENT POSITIONS:**

- Medical Practice – Sleep Medicine, 1994 to present
- Board of Directors, First Community Bank, Inc. 1994 to present, Emeritus
- Associate Clinical Professor, MUSC, Charleston, South Carolina
- Associate Clinical Professor, USC School of Medicine, Columbia, SC
- President, Bogan Consulting Services, PA Charleston, SC
- Owner, Bogan Sleep Consultants, LLC Columbia, SC



**PREVIOUS POSITIONS:**

- Medical Director, Premier Health Systems, Inc.
- Chairman, SleepMed, Inc., 1999-2013
- Chief Medical Officer, Board of Directors, SleepMed Inc. 1999-2020
- National Sleep Foundation Board, 2012 to 2021, Chairman 2019-2021, July 1
- Board of Directors, American Lung Association, South Carolina
- Board of Directors, Premier Health Systems, Inc.
- Medical Director, Baptist Physician Partners

**PROFESSIONAL EXPERIENCE:**

SleepMed, inc  
1999-2020  
Chief Medical Officer

SleepMed, Inc.  
1999 - 2013  
Chairman, CMO

Medical Practice  
1994 - present  
Sleep Medicine

Sleep Disorder Centers of America  
1994 - 1999  
Founder, President

Medical Practice  
1978 - 1994  
Pulmonary and Sleep Medicine

Medical Practice  
1978 - 1994  
Pulmonary

University of Alabama School of Medicine  
1976 - 1978  
Instructor, Department of Medicine

University of Alabama School of Medicine  
1976 - 1978

Fellow, Pulmonary Division, Department of Medicine

University of Alabama School of Medicine

1976 - 1978

Instructor, Pulmonary Division

University of Alabama Hospital and Clinics

1975 - 1976

Chief Resident, Internal Medicine

United States Navy

6/1972 - 6/1974

Lt. Commander, United States Navy

Active duty, Naval Air Station, Albany, GA

#### **PROFESSIONAL ORGANIZATIONS:**

- American Academy of Sleep Medicine
- American College of Chest Physicians
- American Thoracic Society
- South Carolina Medical Association

#### **RESEARCH/SCHOLARLY INTEREST:**

- Narcolepsy
- Insomnia
- Sleep Apnea
- Shift Work Sleep Disorder
- Restless Legs Syndrome/Periodic Limb Movement Disorder
- Chronic Fatigue/Fibromyalgia
- Circadian Rhythm Abnormality
- Pharmacology
- Gas Exchange
- Exercise Physiology

#### **INTERNATIONAL INVITED SPEAKER PRESENTATIONS:**

- Richard K Bogan MD- invited lecturer entitled: Functional Outcomes of CPAP Treated Obstructive Sleep Apnea. IX World Congress on Sleep Apnea Seoul, South Korea; 2009.

- Richard K. Bogan MD Invited lecture: Excessive Daytime Sleepiness: Treatment and Current Best Practices for Idiopathic Hypersomnia, Narcolepsy and Obstructive Sleep Apnea. Mexican Sleep Meeting, Mexico City, Mexico; Oct. 2009.
- Richard K Bogan MD- invited lecturer entitled: Functional Outcomes of CPAP Treated Obstructive Sleep Apnea. The Sino-German Sleep Symposium, Chinese Society of Sleep Medicine; Chengdu 610041, Sichuan Province, China; Oct. 27-Nov.1, 2010.

#### **INVITED SPEAKER PRESENTATIONS:**

- Richard K. Bogan MD-invited lecturer-Cleveland Clinic Sleep Grand Rounds; May 11, 2023.
- Richard K. Bogan MD-invited lecturer entitled: Sleep, Sodium, and CVD: A Cardiology Perspective. Indianapolis, IN; June 3, 2023.
- Richard K. Bogan, MD-invited lecturer- Department of Psychiatry Grand Rounds; August 11, 2023.

#### **PUBLICATIONS:**

- Bogan RK, Roy A, Kram J, Ojile J, Rosenberg R, Hudson JD, Scheuller HS, Winkelman JW, Charlesworth JD. Efficacy and safety of tonic motor activation (TOMAC) for medication-refractory restless legs syndrome: a randomized clinical trial. *Sleep*. 2023 Oct 11;46(10):zsad190. doi: 10.1093/sleep/zsad190. PMID: 37458698; PMCID: PMC10566236.
- Bogan RK, Foldvary-Schaefer N, Skowronski R, Chen A, Thorpy MJ. Long-Term Safety and Tolerability During a Clinical Trial and Open-Label Extension of Low-Sodium Oxybate in Participants with Narcolepsy with Cataplexy. *CNS Drugs*. 2023 Apr;37(4):323-335. doi: 10.1007/s40263-023-00992-y. Epub 2023 Mar 22. PMID: 36947322; PMCID: PMC10126024.
- Cederberg KLJ, Peris Sempere V, Lin L, Zhang J, Leary EB, Moore H, Morse AM, Blackman A, Schweitzer PK, Kotagal S, Bogan R, Kushida CA; STAGES cohort investigator group; Mignot E. Proteomic insights into the pathophysiology of periodic limb movements and restless legs syndrome. *Sleep Health*. 2023 Aug 8;S2352-7218(23)00130-4. doi: 10.1016/j.sleh.2023.06.008. Epub ahead of print. PMID: 37563071.

- Dauvilliers Y, Roth T, Bogan R, Thorpy MJ, Morse AM, Roy A, Dubow J, Gudeman J. Efficacy of once-nightly sodium oxybate (FT218) in narcolepsy type 1 and type 2: post hoc analysis from the Phase 3 REST-ON Trial. *Sleep*. 2023 Nov 8;46(11):zsad152. doi: 10.1093/sleep/zsad152. PMID: 37246913; PMCID: PMC10636255.
- Lacroix J, Tatousek J, Den Teuling N, Visser T, Wells C, Wylie P, Rosenberg R, Bogan R. Effectiveness of an Intervention Providing Digitally Generated Personalized Feedback and Education on Adherence to Continuous Positive Airway Pressure: Randomized Controlled Trial. *J Med Internet Res*. 2023 May 22;25:e40193. doi: 10.2196/40193. PMID: 37213195; PMCID: PMC10242460.
- Mignot E, Bogan RK, Emsellem H, Foldvary-Schaefer N, Naylor M, Neuwirth R, Faessel H, Swick T, Olsson T. Safety and pharmacodynamics of a single infusion of danavorexton in adults with idiopathic hypersomnia. *Sleep*. 2023 Sep 8;46(9):zsad049. doi: 10.1093/sleep/zsad049. PMID: 36883238; PMCID: PMC10485568.
- Morse AM, Dauvilliers Y, Arnulf I, Thorpy MJ, Foldvary-Schaefer N, Chandler P, Chen A, Hickey L, Black J, Bogan RK. Long-term efficacy and safety of low-sodium oxybate in an open-label extension period of a placebo-controlled, double-blind, randomized withdrawal study in adults with idiopathic hypersomnia. *J Clin Sleep Med*. 2023 Oct 1;19(10):1811-1822. doi: 10.5664/jcsm.10698. PMID: 37409509; PMCID: PMC10545992.
- Pittman SD, Chase B, Gottlieb DJ, Hwang D, Kirsch DB, Shah NA, Sterling KL, Thornton K, Barnes TR, Tosi J, Carden KA, Bogan RK, Reuveny A, Ancoli-Israel S and Malhotra A (2024) The future of sleep apnea management: we can either ride the bus or drive it. *Front. Sleep* 2:1323447. doi: 10.3389/frsle.2023.1323447.
- Roth T, Dauvilliers Y, Thorpy MJ, Kushida C, Corser BC, Bogan R, Rosenberg R, Dubow J, Seiden D. Effect of FT218, a Once-Nightly Sodium Oxybate Formulation, on Disrupted Nighttime Sleep in Patients with Narcolepsy: Results from the Randomized Phase III REST-ON Trial. *CNS Drugs*. 2022 Apr;36(4):377-387. doi: 10.1007/s40263-022-00904-6. Epub 2022 Apr 5. PMID: 35380374; PMCID: PMC8994715.
- Roy A, Ojile J, Kram J, Olin J, Rosenberg R, Hudson JD, Bogan RK, Charlesworth JD. Long-term efficacy and safety of tonic motor activation for treatment of medication-refractory restless legs syndrome: A 24-Week Open-Label Extension Study. *Sleep*. 2023 Oct 11;46(10):zsad188. doi: 10.1093/sleep/zsad188. PMID: 37439365; PMCID: PMC10566237.

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## **RESEARCH:**

### **Principal Investigator:**

- Phase III Clinical Investigation Zithromax, 1991
- Phase III Clinical Investigation Centox, 1992
- A Nine-Week, Placebo-Controlled, Double-Blind, Randomized, Parallel-Group Study of the Safety and Efficacy of Two Fixed Doses (200 MG, 400 MG) of Oral Modafinil in Patients with Narcolepsy followed by a 40 Week, Open-Label, Flexible-Dose Continuation Study. 1994-1999. Research results published in the *Annals of Neurology*, January 1998.
- Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Trial Comparing the Effects of Three Doses of Orally Administered Xyrem TM (gamma-hydroxybutyrate) for the Treatment of Narcolepsy Symptoms, 1997-1998.
- Evaluation of the Efficacy and Tolerability of Candesartan Cilexetil in Hypertensive Patients Across Several Aspects of Patient Demographics, 1998-1999.

- Long-Term, Open-Label, Multi-Center Extension Trial of Orally Administered Xyrem™ (gamma-hydroxybutyrate) for the Treatment of Narcolepsy Symptoms, 1998-2002.
- Open-Label, Multi-Center, Six-Month Trial of Xyrem™ (sodium oxybate) Oral Solution for the Treatment of Narcolepsy in Study Drug Naïve Patients, 1999-2000.
- Long-Term, Open-Label, Multi-Center Trial of Orally Administered Xyrem™ (sodium oxybate) Oral Solution for the Treatment of Narcolepsy, 1999-2002.
- A Double-Blind, Placebo-Controlled, Multi-Center, Randomized, Parallel-Group Study of the Effect of Four-Weeks of Provigil® (Modafinil) Treatment on Excessive Daytime Sleepiness in Obstructive Sleep Apnea Patients Treated with Nasal Continuous Positive Airway Pressure, 1999-2000.
- A Double-Blind Study Comparing Daily Doses of 200mg and 400mg of Oral PROVIGIL® (Modafinil) Using a Full-Day Profile of the Maintenance of Wakefulness Test in Patients with Narcolepsy Taking 1 of 3 Doses (200mg Once Daily, 400mg Once Daily, and 200mg Twice Daily), 2000.
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- A Double-Blind, Placebo-Controlled Parallel Randomized Study of the Efficacy and Safety of (S)-Zopiclone in the Treatment of Adult Patients with Primary Insomnia, 2000-2001.
- Management of Excessive Daytime Sleepiness in Narcolepsy, 2000-2002.
- A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Impact on Quality of Life of 12 Weeks of PROVIGIL® (Modafinil) Therapy at Dosages of 200 and 300mg Once Daily as Treatment for Adults with Excessive Sleepiness Associated with Shift Work Sleep Disorder, Followed by a 12-Month Open-Label Extension Period, 2000-2002.
- A Randomized, Double-Blind, Placebo-Controlled, Dose-Response Study to Assess the Efficacy and Safety of a Modified Release Formulation of NBI-34060-MR-0102 in Patients with Chronic Sleep Maintenance Insomnia, 2001-2002.
- An Efficacy, Safety, and Dose Response Study of TAK-375 in Subjects with Chronic Insomnia, 2001-2002.

- A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of 12 Weeks of PROVIGIL® (Modafinil) Therapy at a Dose of 200 mg as Treatment for Adults with Excessive Sleepiness Associated with Chronic Shift Work Sleep Disorder, Followed by a 12-Month Open-Label Extension Period, 2001-2003.
- A Randomized, Double-Blind, Placebo-Controlled Parallel, Two Week Objective Efficacy and Safety Study of Esopiclone in Elderly Subjects with Primary Insomnia, 2001-2002.
- A Randomized, Double-Blind, Placebo-Controlled, Dose-Response Study to Assess the Efficacy and Safety of a Modified Release Formulation of NBI-34060-MR-0103 in Elderly Patients with Chronic Sleep Maintenance Insomnia, 2002.
- Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Trial Comparing the Effects of Orally Administered Xyrem® (sodium oxybate) with Placebo for the Treatment of Narcolepsy, 2002-2004.
- A 12-Week, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Efficacy, Safety and Tolerability of Ropinirole in Subjects with Restless Legs Syndrome (RLS) Suffering from Periodic Limb Movements of Sleep (PLMS), 2002.
- Comparison of efficacy and safety of zolpidem-MR 12.5 mg and placebo in patients with primary insomnia. A double-blind, randomized, placebo-controlled, parallel-group study, 2002-2003.
- A Phase III, Randomized, Double-Blind, Placebo-Controlled, Outpatient Study to Assess the Long-Term Safety and Efficacy of Two Dose Levels of NBI-34060 in Adult Patients With primary Insomnia, 2002-2003.
- Open-Label, Multi-Center Safety Trial Studying the Effects of Orally Administered Xyrem (Sodium Oxybate), 2002-2004.
- A Randomized, Double-Blind, Active and Placebo Controlled 4-Way Crossover Study of the Safety and Efficacy of PD 0200390, Zolpidem, and Placebo in Primary Insomnia (Protocol A4251003), 2002.
- A Phase III, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Determine the Safety and Efficacy of TAK-375 in Elderly Subjects with Chronic Insomnia, 2002-2003.
- A Phase III, Open Label, Fixed-Dose Study to Determine the Safety of Long-Term Administration of TAK-375 in Subjects with Chronic Insomnia, 2002-2004.

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- A Six-Month, Chronic Efficacy and Safety Study of Eszopiclone in Adult Subjects with Primary Insomnia: A Randomized Double-Blind, Placebo-Controlled Study, 2003-2004.



- A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter, Fixed-Dose, Polysomnographic Study of PD 0200390 in Patients with Primary Insomnia, 2003-2004.
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- A North American, 4-Week, Multicenter, Phase IIB Double-Blind, Placebo-Controlled, Randomized, Multiple Dose, Parallel-Group Study of the Efficacy and Safety of 0.5 mg, 1.0 mg and 2.0 mg M100907 Tablets in the Treatment of Sleep Maintenance Insomnia, 2004.
- A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of PROVIGIL<sup>®</sup> (Modafinil) Treatment (100, 200, and 400 mg/day) in Children and Adolescents with Excessive Sleepiness Associated with Narcolepsy, 2004-2006.
- A 1-Year Open-Label, Flexible-Dosage Extension Study to Assess the Safety and Continued Effectiveness of PROVIGIL<sup>®</sup> (Modafinil) Treatment in Children and Adolescents with Excessive Sleepiness Associated with Narcolepsy or Obstructive Sleep Apnea/Hypopnea Syndrome, 2004-2006.
- A Double-Blind, Randomized, Placebo-Controlled, Multicenter, 30-Night Polysomnographic Study of MK-0928 in Elderly Patients with Primary Insomnia, 2004-2006.



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- Evaluation of the long-term efficacy and safety of zolpidem-MR 12.5-mg compared to placebo, when both are administered over a long-term period “as needed”, in patients with chronic primary insomnia. (A randomized, double-blind, placebo-controlled, parallel group, multicentre, phase IIIb clinical study), 2004-2005.
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- A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of CEP-10953 (150 and 250 mg/day) as Treatment for Adults with Residual Excessive Sleepiness Associated with Obstructive Sleep Apnea/Hypopnea Syndrome, 2004.
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- A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter, Study of MK-0928 in Healthy Adult Volunteers Participating in a 4-hour Phase Advance Model of Transient Insomnia, 2005-2006.
- A Short-Term (8-Week) Open-Label Study, followed by a Long-Term Evaluation, To Assess Patient Satisfaction with Armodafinil Treatment (150 to 250 mg/day) for Excessive Sleepiness in Adults with Narcolepsy or Obstructive Sleep Apnea / Hypopnea Syndrome (OSAHS), 2005-2006.
- A Randomized, Double-Blind, Placebo-Controlled Study to Determine the Long-Term Efficacy and Safety of Ramelteon in Adults with Chronic Insomnia, 2006.

- A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Efficacy and Multiple-Dose Plasma Concentration-Time Profiles of Armodafinil (150, 200, and 250 mg) and Provigil® (200 mg) in Patients with Chronic Shift Work Sleep Disorder, 2006.
- A 52-Week, Open-Label Study to Assess the Long-Term Safety of Ropinirole Extended Release (XR) in Patients with Restless Legs Syndrome (RLS), 2005-2007.
- A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study to Evaluate Effects of the APD125 in Patients with Insomnia, 2005-2007.
- An Open-Label Extension Trial to Investigate the Safety and Tolerability of Long-Term Treatment with Transdermal Rotigotine in Subjects with Idiopathic Restless Legs Syndrome, 2005-2007.
- A 4-Week, Randomized, Double-Blind, Cohort Study to Evaluate the Safety and Tolerability of Converting from Ropinirole Immediate Release (IR) to Ropinirole Extended Release (XR) Formulation in Patients with Restless Legs Syndrome (RLS), 2006.
- Efficacy and Safety of Eplivanserin 5mg/day on Sleep Maintenance Insomnia: a 6-week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study, 2006 – 2007.
- A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Study to Investigate the Efficacy and Safety of a Single Oral Dose of VEC-162 (20, 50, and 100 mg) and Matching Placebo in Healthy Male and Female Subjects with Induced Transient Insomnia, 2006.
- A 28 day, Polysomnographic and Subjective Assessment of GW679769, 10 and 30 mg, for the Treatment of Primary Insomnia: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial, 2006 – 2007.
- A Long-Term Study of XP13512 vs. Placebo Treatment Assessing Maintenance of Efficacy and Safety in Patients with Restless Legs Syndrome, 2006 – 2008.
- A Phase III, Randomized, Double-Blind, Placebo-Controlled, Outpatient Study to Assess the Long-Term Safety and Efficacy of Two Dose Levels of NB1-34060 in Adult Patients with Primary Insomnia, 2006.
- A Randomized, Double-Blind Comparison of 5 mg of LY2422347, 15 mg of LY2422347, and Placebo in the Treatment of Patients with Primary Insomnia, 2006.

- A phase IV randomized, double-blind, active and placebo-controlled, 6-week trial to investigate the efficacy and safety of a starting (and fixed) dose of 0.25 mg Pramipexole (Mirapex) in patients w idiopathic Restless Legs Syndrome, 2006-2007.
- Switch: An open Label Prospective Study of Restless Legs Patients Switched to Ropinirole from Pramipexole To Help Determine the Equipotent Dose, 2006-2007.
- Efficacy and Safety of eplivanserin 5mg/day on Sleep Maintenance Insomnia: a 12-week multicenter, randomized, double-blind, placebo-controlled study followed by an open treatment phase extension with eplivanserin for 40 weeks period, 2006-2007.
- A phase 2, Double-blind, randomized, placebo-controlled, parallel-group, Multicenter Proof-of-Concept Study to Evaluate the Safety and Efficacy of Ramelteon Taken in Combination with Doxepin for the Treatment of Subjects with Chronic Insomnia, 2006-2007.
- A Phase II Randomized, Double-blind, Double-dummy, Placebo and Comparator-Controlled, Parallel Group, Multi-Center Study to Investigate the Safety and Efficacy of a Single Dose of JNJ-17216498 Administered to Subjects with Narcolepsy, 2006-2008.
- A randomized, multicenter, double-blind, placebo-controlled, parallel group study to assess the hypnotic efficacy of EVT201 in the treatment of primary insomnia in elderly patients with daytime sleepiness, 2006.
- A 12-week, Multi-Center, Double-Blind, Placebo-Controlled, Parallel Group, Flexible Dose Polysomnography Study of Ropinirole and Periodic Limb Movements (PLM) During Sleep, 2006.
- A multi-center, randomized, open-label, active controlled, parallel arm study to compare the efficacy of 12 weeks of treatment with Vildagliptin 100 mg, qd to thiazolidinedione (TZD) as add-on therapy in patients with type 2 diabetes inadequately controlled with Metformin monotherapy in a community-based practice, 2006-2007.
- A Randomized, Double-Blind, Placebo-Controlled Dose-Response Study to Assess the Efficacy, Safety, and Pharmacokinetics of XP13512 in Patients with Restless Legs Syndrome, 2006-2007.
- An Open-Label, 52-Week Extension Study Assessing XP13512 Safety and Efficacy in Patients with Restless Legs Syndrome, 2007-2008.

- A Randomized, Double-Blind, Placebo-Controlled, Parallel, Proof of Concept Study to Evaluate the Effectiveness of Ramelteon to Advance the Timing of Sleep in individuals with Delayed Sleep Phase Syndrome (DSPS), 2007-2008.
- A Randomized, Double Blind, Placebo-Controlled, Parallel Group Study to Demonstrate the Subjective Treatment Effects of Ramelteon on Sleep Using a Post Sleep Questionnaire – Interactive Voice Response System (PSQ-IVRS) in an “At-Home Setting” in an Adult Population with Chronic Insomnia, 2007.
- Multicenter, double-blind, randomized, placebo-controlled, 5-period, 5-treatment crossover, dose-finding study to evaluate the efficacy and safety of oral administration of ACT-078573 in elderly subjects with chronic primary insomnia, 2007.
- A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Armodafinil at a Target Dosage of 200 mg/day as Treatment for Adults with Excessive Sleepiness Associated with Obstructive Sleep Apnea/Hypopnea Syndrome with Comorbid Major Depressive Disorder or Dysthymic Disorder, 2007 – 2009.
- A Randomized, Double-blind, Placebo-controlled Subjective Study to Assess the Efficacy of APD125 in Patients with Primary Insomnia Characterized by Difficulty Maintaining Sleep, 2008.
- A Randomized, Double-Blind, Parallel Group, Placebo-controlled, Multicenter Outpatient Trial of PD 0200390 in Adults with Nonrestorative Sleep, 2008.
- A Three-Group Proof-Of-Principal Study to Evaluate and Compare Different Biometric Technologies Designed to Assess Quality of Sleep in Healthy Subjects, 2008.
- A 3-Day, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Effect of Armodafinil Treatment (50 and 150 mg/day) in Healthy Subjects with Excessive Sleepiness Associated with Jet Lag Disorder, 2008-2009.
- A polysomnography study of GSK1838262 (XP13512) sustained release tablets versus placebo in the treatment of Restless Legs Syndrome (RLS) and associated sleep disturbance, 2008-2009.
- Efficacy and safety of eplivanserin 5 mg/day in insomnia characterized by sleep maintenance difficulties: a 6-week, randomized, double-blind, placebo-controlled, polysomnography study, 2008-2009.
- A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-Dosage Study to Evaluate the Efficacy and Safety of Armodafinil (50, 150,

and 250 mg/day) as Treatment for Patients with Excessive Sleepiness Associated with Mild or Moderate Closed Traumatic Brain Injury, 2009 –2010.

- A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel- Group, Long-Term Safety Study of MK-4305 in Patients with Primary Insomnia, 2009 –2011.
- A Phase IIb, Multicenter, Randomized, Double-Blind, Placebo-Controlled, 2-Period Adaptive Crossover Polysomnography Study to Evaluate the Safety and Efficacy of MK-6096 in Patients with Primary Insomnia, 2009 –2011.
- A Randomized, Double-Blind, Placebo-Controlled, 3-Way Crossover, Multicenter Polysomnography Study of Pregabalin And Pramipexole In Adults with Restless Legs Syndrome, 2009 –2011.
- Effects of Pregabalin On Sleep Maintenance in Subjects with Fibromyalgia Syndrome and Sleep Maintenance Disturbance: A Randomized Placebo-Controlled 2-Way Crossover Polysomnography Study, 2009 –2010.
- Pfizer 1015. Randomized Phase 2, Double-Blind, Placebo-Controlled, Cross-over Multicenter Study of PF-0365746 as a daily treatment for excessive sleepiness (EDS) Associated with Narcolepsy 2009-2012.
- Randomized, Double-Blind, 12-Month Study of Pregabalin In Subjects with Restless Legs Syndrome, 2009 –2012
- A prospective, multicenter, parallel group, sham-controlled, randomized, double-blinded clinical trial to compare the safety and effectiveness of the Provent<sup>TM</sup> Professional Sleep Apnea Therapy device to sham for the non-invasive treatment of obstructive sleep apnea-hypopnea, 2009 –2012
- Is Adaptive Servo-Ventilation Therapeutically More Effective Than Continuous Positive Airway Pressure in Treating Complex Sleep Apnea Syndrome? 2009 – 2012.
- GSK Summit: A Clinical Outcomes Study to Compare the Effect of Fluticasone Furoate/Vilanterol Inhalation Powder 100/25 mcg with Placebo on Survival of Subjects with Moderate Chronic Obstructive Pulmonary Disease (COPD) and an history of increased risk for cardiovascular disease 2010-2011.
- A Randomized, Double-Blind, Sham-Controlled, Multicenter Study of the Symphony<sup>TM</sup> Counter-stimulation Device in Restless Legs Syndrome, 2009.
- Cephalon 3067: A Twelve Week: Randomized, Double-Blind placebo-controlled, Parallel- Group Fixed Dosage Study to Evaluate the Efficacy and Safety of Armodafinil (50, 150, and 250mg/day) as Treatment for Patients with excessive

- sleepiness associated with Mild to Moderate Closed Traumatic Brain Injury, 2009-2010.
- IMPAX RLS: A Randomized, Double-Blind, Placebo-Controlled Safety and Efficacy Study of IPX 159 in the treatment of Moderate to Severe Restless Legs Syndrome. 2011-2013.
  - Merck 6096 Phase IIb Double Blind placebo-controlled 2 period adaptive crossover PSG study to evaluate the safety and efficacy in patients with insomnia, 2009-2011.
  - Merck 4305 Phase III Double Blind placebo-controlled parallel long-term safety study in patients with primary insomnia 2009-2011.
  - VSOM: The effect of Vestibular stimulation on chronic insomnia 2009-2011.
  - Cephalon 4030, Double Blind placebo-controlled to Evaluate the Efficacy and Tolerability of Armodafinil Treatment in improving clinical condition late in the shift and improving patient reported outcomes in adult patients with excessive sleepiness associated with shift worker sleep disorder, 2010-2011.
  - Glycosa/ResMed: Effect of CPAP Treatment on Glycemic Control in patients with Type II Diabetes Mellitus and Obstructive Sleep Apnea 2010-2012.
  - Vanda: A Multicenter Randomized Double-Blind Placebo Controlled Parallel Study to Investigate the Efficacy and Safety of 20mg Tasimelon Versus Placebo in totally blind Subjects with N2HSWD Followed by an OLE Phase 2011-2014.
  - APNEX: Pivotal Study of the Apex Medical Hypoglossal Nerve Stimulation (HGNS) system to treat Obstructive Sleep Apnea 2011-2013.
  - AERIAL: A four week, Double-blind, placebo-controlled, randomized, cross-over study of the safety and efficacy of ADX-N05 in the treatment of excessive daytime sleepiness 2011-2013.
  - AERIAL: A twelve week, Double-blind, placebo-controlled, randomized, parallel-group study of the efficacy of ADX-NO5 in the treatment of excessive daytime sleepiness in subjects with narcolepsy 2012-2013.
  - APNICURE FIT II: A Multicenter Prospective Variable Duration, Reiterative Development and Evaluation Study of ApniCure's Therapy System (s) for the Treatment of Obstructive Sleep Apnea. 2009-2011.

- APNICURE FIT III: A Multicenter Prospective Variable Duration, Reiterative Development and Evaluation Study of ApniCure's Therapy System (s) for the Treatment of Obstructive Sleep Apnea. 2012-2014.
- ATLAST Long-Term: A Multicenter Prospective Long-Term Study of the Attune Sleep Apnea System for the Treatment of Obstructive Sleep Apnea 2011-2013.
- CONCORD: A Randomized Double-Blind Placebo-Controlled Fixed Dose, Parallel Group Study to Compare Efficacy, Tolerability and Safety of 3 Doses of Gabapentin Enacarbil (GSK 1838262) With Placebo in the Treatment of Subjects with Moderate –To-Severe Restless Legs Syndrome (RLS) 2012-2013
- SCALE <sup>TM</sup>. Sleep Apnoea: Effect of Liraglutide in Obese Subjects with Moderate or Severe Obstructive Sleep Apnea. A 32-week randomized. Double-blind, placebo-controlled, parallel group, multi-center and multinational trial parallel group, multi-center and multinational trial. 2012-2013.
- Fisher and Paykel Healthcare FPH-083-01: Comparison study of the ICON <sup>TM</sup> CPAP series with and without Sens Awake <sup>TM</sup> 2013-2014.
- Eisai E 2006-G000-201: A Multicenter, randomized. Double-blind, placebo-controlled, parallel –group, Bayesian adaptive, randomization design, dose response study of the efficacy of E2006 in Adults and Elderly subjects with chronic insomnia. 2013-2014.
- BIG4CPAP (Phillips Respironics) PGI-BIG4-1331-MS): Educational Materials and Usage Feedback to Promote CPAP Adherence, 2013-2014.
- A Twelve-week, Double-blind, Placebo-controlled, Randomized, Parallel-group, Multicenter Study of the Safety and Efficacy of JZP-110 in the Treatment of Excessive Sleepiness in Subjects with Narcolepsy, Ph III,(JAZZ Pharmaceuticals, 2014-2015)
- A Twelve-week, Double-Blind, Placebo-Controlled, Randomized, Parallel-Group, Multicenter Study of the Safety and Efficacy of JZP-110 in the Treatment of Excessive Sleepiness in Subjects with Obstructive Sleep Apnea (OSA), Ph III,(JAZZ Pharmaceuticals, 2014-2015)
- A Randomized, Placebo-Controlled, Double-blind, Fixed-Dose, Multiple Cohort, Multiple Crossover, Dose-Finding Study of Oral BTD-001 in Adults with Idiopathic Hypersomnia or Narcolepsy Type 2, PhIIb, (Balance Therapeutics, Inc., 2015)
- A Double-Blind, Placebo-Controlled, Randomized-Withdrawal, Multicenter Study of the Efficacy and Safety of Xyrem with an Open-Label Pharmacokinetic



Evaluation and Safety Extension in Pediatric Subjects with Narcolepsy with Cataplexy, PhII/III, (JAZZ Pharmaceuticals, 2014-2015)

- A Multicenter, Open-Label, Single-Dose Pharmacokinetic and Safety Evaluation of HORIZANT in Adolescents Aged 13-17 Years Old with Moderate-to-Severe Restless Legs Syndrome, Ph I (XenoPort, Inc., 2015)
- A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Parallel-Group Study of the Efficacy and Safety of Lemborexant in Subjects 55 and Older with Insomnia Disorder, PhIII, (EISAI Inc., 2016, E2006-G000-304).
- EXPRESS (Jazz 13-005): A Randomized, Double-Blind, Placebo-Controlled, Randomized –Withdrawl Multicenter Study of the Efficacy and Safety of Xyrem in an Open-Label Pharmacokinetic Evaluation and Safety Extension in Pediatric Subjects with Narcolepsy and Cataplexy. 2014-2017
- A Phase 2, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of 2 mg and 4 mg SUVN-G3031 Compared to Placebo in Patients with Narcolepsy with and without Cataplexy. 2019- Present
- An Open Label Study to Evaluate Long-Term Safety and Tolerability of a Once Nightly Formulation of Sodium Oxybate for Extended-Release Oral Suspension (FT218) and the Ability to Switch from Twice Nightly Immediate Release Sodium Oxybate or Mixed Salts Oxybate to Once Nightly FT218 for the Treatment of Excessive Daytime Sleepiness and Cataplexy in Subjects with Narcolepsy. 2020- Present
- A Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of PRM-151 in Patients with Idiopathic Pulmonary Fibrosis. 2022-2023
- Diagnostic validation of the DreamKit device against polysomnography. 2021-2022
- A Phase 4 Multicenter, Open-label, Single-arm Study of Safety, Tolerability, Effectiveness and Treatment Optimization in Participants Switching From Xyrem to XYWAV for the Treatment of Narcolepsy. 2021-2023
- Solriamfetol's Effect on Cognitive Health in Apnea Participants During a Randomized Placebo-controlled Study (SHARP): a 5-Week Double-blind, Placebo-controlled, Randomized, Crossover, Multicenter Study of Solriamfetol in Improving Cognitive Function in Participants With Excessive Daytime Sleepiness Associated With Obstructive Sleep Apnea Plus Impaired Cognitive Function. 2021-2022



- Treating Obstructive Sleep Apnea using Targeted Hypoglossal Neurostimulation. 2021- Present
- Randomized, double-blind, placebo-controlled, parallel-group Phase 3 study to evaluate the efficacy, safety, and tolerability of SAR440340/REGN3500/itepekimab (anti-IL-33 mAb) in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD). 2021-Present
- A Four-week, Double- blind, Placebo-controlled, Randomized, Multicenter, Parallel-group Study of the Safety and Efficacy of NLS-2 (Mazindol extended release) in Adults for the Treatment of Narcolepsy. 2021-2022
- A 6-Month Multicenter, Open-Labelled Extension of the Clinical Trial NLS-1021 in Narcoleptic Patients with and without Cataplexy. 2021- Present
- Use of the ExVent Accessory with the O2 Vent Optima Oral Appliance for the Treatment of Obstructive Sleep Apnea. 2021-Present
- A randomized, double-blind, placebo controlled study assessing the long-term effect of dupilumab on prevention of lung function decline in patients with uncontrolled moderate to severe asthma. 2022-Present
- A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Doses of TAK-861 in Healthy Adult and Elderly Subjects and Subjects With Narcolepsy Type 1. 2022-Present
- Bogan - OURA Overnight OA11 Protocol. 2023-Present
- Randomized Double-Blind 2-Period Multiple Dose Crossover Study to Evaluate the Efficacy and Safety of AD113 (atomoxetine/spironolactone) vs atomoxetine in OSA patients with hypertension. 2022-Present
- A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy and Safety of AXS-12 in the Treatment of Cataplexy and Excessive Daytime Sleepiness in Subjects with Narcolepsy. 2021-Present
- A Study to Assess the Long-term Efficacy and Safety of AXS-12 in the Treatment of Cataplexy and Excessive Daytime Sleepiness in Subjects with Narcolepsy. 2021-Present
- A Double-Blind, Placebo Controlled, Randomized Withdrawal Study to Evaluate the Safety and Efficacy of Pitolisant in Adult Patients with Idiopathic Hypersomnia. 2022-Present

- An Open-Label Study to Evaluate the Long-Term Safety and Effectiveness of Pitolisant in Adult Patients with Idiopathic Hypersomnia who Completed HBS-101-CL-010. 2022-Present
- Multi-center, double-blind, randomized, placebo-controlled, parallel-group, polysomnography, dose-finding study assessing the efficacy, safety, and pharmacokinetics of multiple-dose oral administration of daridorexant in pediatric subjects aged 10 to < 18 years with insomnia disorder. 2022-Present
- A Phase 2, Placebo-Controlled, Double-Blind, Randomized Withdrawal Study to Determine the Safety and Efficacy of Oral SDX in Patients with Idiopathic Hypersomnia (IH). 2023-Present
- An open-label randomized controlled trial assessing the efficacy of intraoral neuromuscular electrical stimulation for treatment of mild obstructive sleep apnea: The OREM Trial. 2022-Present
- Study Using Negative Pressure to Reduce Apnea (SUPRA). 2021-Present
- A Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK- 861 for the Treatment of Narcolepsy With Cataplexy (Narcolepsy Type 1). 2023-Present
- A Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-861 for the Treatment of Narcolepsy Without Cataplexy (Narcolepsy Type 2). 2023-Present
- A Long-term Extension Study to Evaluate the Safety and Tolerability of TAK-861 in Participants With Selected Central Hypersomnia Conditions. 2023-Present
- A multicenter, double-blind, randomized study to evaluate the effects of tasimelteon vs. placebo in participants with Delayed Sleep-Wake Phase Disorder (DSWPD). 2021-Present
- A Study to Evaluate the Efficacy and Safety of Tasimelteon in Treating Sleep Disturbances in Individuals with Autism Spectrum Disorder. 2022-Present

# **EXHIBIT B**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

LUMRYZ (sodium oxybate) for extended-release oral suspension, CIII  
Initial U.S. Approval: 2002

**WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION AND ABUSE AND MISUSE**

*See full prescribing information for complete boxed warning.*

**Central Nervous System Depression**

• LUMRYZ is a CNS depressant, and respiratory depression can occur with LUMRYZ use (5.1, 5.4)

**Abuse and Misuse**

• LUMRYZ is the sodium salt of gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma, and death (5.2, 9.2)

LUMRYZ is available only through a restricted program called the LUMRYZ REMS (5.3)

**RECENT MAJOR CHANGES**

Indications and Usage (1)	10/2024
Dosage and Administration (2.2)	10/2024
Warnings and Precautions (5.4, 5.5, 5.6, 5.7)	10/2024

**INDICATIONS AND USAGE**

LUMRYZ is a central nervous system depressant indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy (1).

**DOSAGE AND ADMINISTRATION**

**Dosing for Adults:**

- Initiate dosage at 4.5 g once per night orally (2.1).
- Titrate to effect in increments of 1.5 g per night at weekly intervals (2.1).
- Recommended dosage range: 6 g to 9 g once per night orally (2.1).

**Dosing for Pediatric Patients (7 Years of Age and Older):**

- The recommended starting dosage, titration regimen, and maximum total nightly dosage are based on body weight (2.2)
- *Pediatric patients 7 years and older weighing at least 45 kg:* The recommended starting dosage is 4.5 g once per night. Increase the dosage by 1.5 g per night at weekly intervals to the maximum recommended dosage of 9 g once per night orally. The dosage may be gradually titrated based on efficacy and tolerability (2.2).
- *Pediatric patients 7 years and older weighing less than 45 kg:* Because the recommended starting dosage cannot be achieved with the available strengths of LUMRYZ, use another sodium oxybate product to initiate treatment (2.2).

- Prepare the dose of LUMRYZ prior to bedtime; suspend dose in approximately ½ cup of water in the mixing cup provided (2.3).
- Allow 2 hours after eating before dosing (2.3).
- Take LUMRYZ while in bed and lie down after dosing (2.3).

**DOSAGE FORMS AND STRENGTHS**

For extended-release oral suspension: Packets of 4.5 g, 6 g, 7.5 g, or 9 g (3)

**CONTRAINDICATIONS**

- In combination with sedative hypnotics or alcohol (4).
- Succinic semialdehyde dehydrogenase deficiency (4).

**WARNINGS AND PRECAUTIONS**

- CNS depression: Use caution when considering the concurrent use of LUMRYZ with other CNS depressants (5.1).
- Caution patients against hazardous activities requiring complete mental alertness or motor coordination within the first 6 hours of dosing or after first initiating treatment until certain that LUMRYZ does not affect them adversely (5.1).
- Depression and suicidality: Monitor patients for emergent or increased depression and suicidality (5.5).
- Confusion/Anxiety: Monitor for impaired motor/cognitive function (5.6).
- Parasomnias: Evaluate episodes of sleepwalking (5.7).
- High sodium content in LUMRYZ: Monitor patients with heart failure, hypertension, or impaired renal function (5.8).

**ADVERSE REACTIONS**

Most common adverse reactions in adults (incidence ≥ 5% and greater than placebo) reported for any dose of LUMRYZ were nausea, dizziness, enuresis, headache, and vomiting (6.1).

Most common adverse reactions for pediatric patients (≥ 5%) in a study with immediate-release sodium oxybate were nausea, enuresis, vomiting, headache, weight decreased, decreased appetite, dizziness, and sleepwalking (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Avadel CNS Pharmaceuticals, LLC at 1-888-828-2335 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Geriatric patients: Monitor for impaired motor and/or cognitive function when taking LUMRYZ (8.5).
- Hepatic Impairment: Because of an increase in exposure, LUMRYZ should not be initiated in patients with hepatic impairment because appropriate dosage adjustments for initiation of LUMRYZ cannot be made (8.6).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2024

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## FULL PRESCRIBING INFORMATION

### **WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION AND ABUSE AND MISUSE**

#### **Central Nervous System Depression**

LUMRYZ (sodium oxybate) is a CNS depressant. Clinically significant respiratory depression and obtundation may occur in patients treated with LUMRYZ at recommended doses [see *Warnings and Precautions* (5.1)]. Many patients who received sodium oxybate during clinical trials in narcolepsy were receiving central nervous system stimulants [see *Clinical Trials* (14)].

#### **Abuse and Misuse**

LUMRYZ (sodium oxybate) is the sodium salt of gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death [see *Warnings and Precautions* (5.2)].

Because of the risks of CNS depression and abuse and misuse, LUMRYZ is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the LUMRYZ REMS [see *Warnings and Precautions* (5.3)].

## **1 INDICATIONS AND USAGE**

LUMRYZ is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Adult Dosing Information**

The recommended starting dosage of LUMRYZ in adults is 4.5 grams (g) once per night administered orally. Increase the dosage by 1.5 g per night at weekly intervals to the recommended dosage range of 6 g to 9 g once per night orally. The dosage may be gradually titrated based on efficacy and tolerability. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.

### **2.2 Pediatric Dosing Information**

The recommended starting pediatric dosage, titration regimen, and maximum total nightly dosage are based on patient weight.

Pediatric Patients 7 years and Older Weighing at least 45 kg

The recommended starting dosage of LUMRYZ in pediatric patients 7 years and older weighing at least 45 kg is 4.5 g once per night administered orally. Increase the dosage by 1.5 g per night at weekly intervals to the maximum recommended dosage of 9 g once per night orally. The dosage may be gradually titrated based on efficacy and tolerability.

#### Pediatric Patients 7 years and Older Weighing Less than 45 kg

Because the recommended starting dosage in pediatric patients 7 years and older weighing less than 45 kg cannot be achieved with the available strengths of LUMRYZ, use another sodium oxybate product to initiate treatment. Refer to the Prescribing Information of other sodium oxybate products for the recommended dosage for those products.

The maximum recommended dosage for patients 7 years and older weighing 20 kg to <30 kg is 6 g once per night orally, and the maximum recommended dosage for patients 7 years and older weighing 30 kg to <45 kg is 7.5 g once per night orally [*see Dosage and Administration (2.4)*]. There is insufficient information to provide specific dosing recommendations for patients 7 years and older who weigh less than 20 kg.

### **2.3 Important Administration Instructions**

LUMRYZ is taken orally as a single dose at bedtime. Prepare the dose of LUMRYZ prior to bedtime. Prior to ingestion, the dose of LUMRYZ should be suspended in approximately 1/3 cup (approximately 80 mL) of water in the mixing cup provided [*see Instructions for Use*]. Do not use hot water [*see Clinical Pharmacology (12.3)*]. After mixing, consume LUMRYZ within 30 minutes.

Take LUMRYZ at least 2 hours after eating [*see Clinical Pharmacology (12.3)*].

Patients should take LUMRYZ while in bed and lie down immediately after dosing as LUMRYZ may cause them to fall asleep abruptly without first feeling drowsy. Patients will often fall asleep within 5 minutes of taking LUMRYZ, and will usually fall asleep within 15 minutes, though the time it takes any individual patient to fall asleep may vary from night to night. Patients should remain in bed following ingestion of LUMRYZ.

### **2.4 Switching Patients from Immediate-Release Sodium Oxybate**

Patients who are currently being treated with immediate-release sodium oxybate may be switched to LUMRYZ at the nearest equivalent dosage in grams per night (e.g., 7.5 g sodium oxybate divided into two 3.75 g doses per night to 7.5 g LUMRYZ once per night).

## **3 DOSAGE FORMS AND STRENGTHS**

For extended-release oral suspension: LUMRYZ is a white to off-white powder provided in packets of 4.5 g, 6 g, 7.5 g, or 9 g of sodium oxybate.

## **4 CONTRAINDICATIONS**

LUMRYZ is contraindicated for use in:

- combination with sedative hypnotics [*see Warnings and Precautions (5.1)*]

- combination with alcohol [*see Warnings and Precautions (5.1)*]
- patients with succinic semialdehyde dehydrogenase deficiency [*see Clinical Pharmacology (12.3)*]

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Central Nervous System Depression**

LUMRYZ is a central nervous system (CNS) depressant. Clinically significant respiratory depression and obtundation has occurred in patients treated with immediate-release sodium oxybate at recommended doses in clinical trials and may occur in patients treated with LUMRYZ at recommended doses. LUMRYZ is contraindicated in combination with alcohol and sedative hypnotics. The concurrent use of LUMRYZ with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating antiepileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. If use of these CNS depressants in combination with LUMRYZ is required, dose reduction or discontinuation of one or more CNS depressants (including LUMRYZ) should be considered. In addition, if short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with LUMRYZ should be considered. In addition to coadministration of LUMRYZ and alcohol being contraindicated because of respiratory depression, consumption of alcohol while taking LUMRYZ may also result in a more rapid release of the dose of sodium oxybate [*see Clinical Pharmacology (12.3)*].

Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that LUMRYZ does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking LUMRYZ. Patients should be queried about CNS depression-related events upon initiation of LUMRYZ therapy and periodically thereafter.

LUMRYZ is available only through a restricted program under a REMS [*see Warnings and Precautions (5.3)*].

### **5.2 Abuse and Misuse**

LUMRYZ is a Schedule III controlled substance. The active ingredient of LUMRYZ, sodium oxybate, is the sodium salt of gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with the amnestic features of GHB, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim). Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB



(e.g., increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy) [*see Warnings and Precautions (5.3) and Drug Abuse and Dependence (9.2)*].

LUMRYZ is available only through a restricted program under a REMS [*see Warnings and Precautions (5.3)*].

### **5.3 LUMRYZ REMS**

LUMRYZ is available only through a restricted distribution program called the LUMRYZ REMS because of the risks of central nervous system depression and abuse and misuse [*see Warnings and Precautions (5.1, 5.2)*].

Notable requirements of the LUMRYZ REMS include the following:

- Healthcare providers who prescribe LUMRYZ are specially certified.
- LUMRYZ will be dispensed only by pharmacies that are specially certified.
- LUMRYZ will be dispensed and shipped only to patients who are enrolled in the LUMRYZ REMS with documentation of safe use conditions.

Further information is available at [www.LUMRYZREMS.com](http://www.LUMRYZREMS.com) or by calling 1-877-453-1029.

### **5.4 Respiratory Depression and Sleep-Disordered Breathing**

LUMRYZ may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses of oxybate and with illicit use of GHB, life-threatening respiratory depression has been reported [*see Overdosage (10)*].

Increased apnea and reduced oxygenation may occur with LUMRYZ administration. A significant increase in the number of central apneas and clinically significant oxygen desaturation may occur in patients with obstructive sleep apnea treated with LUMRYZ.

During polysomnographic evaluation (PSG), central sleep apnea and oxygen desaturation were observed in pediatric patients with narcolepsy treated with immediate-release sodium oxybate.

In adult clinical trials of LUMRYZ in patients with narcolepsy, no subjects with apnea/hypopnea indexes greater than 15 were allowed to enroll.

In an adult study assessing the respiratory-depressant effects of immediate-release sodium oxybate at doses up to 9 g per night in 21 patients with narcolepsy, no dose-related changes in oxygen saturation were demonstrated in the group as a whole. One of four patients with preexisting moderate-to-severe sleep apnea had significant worsening of the apnea/hypopnea index during treatment.

In an adult study assessing the effects of immediate-release sodium oxybate 9 g per night in 50 patients with obstructive sleep apnea, immediate-release sodium oxybate did not increase the severity of sleep-disordered breathing and did not adversely affect the average duration and severity of oxygen desaturation overall. However, there was a significant increase in the number of central apneas in patients taking immediate-release sodium oxybate, and clinically significant oxygen desaturation ( $\leq 55\%$ ) was measured in three patients (6%) after administration, with one patient withdrawing from the study and two continuing after single brief instances of desaturation.

In adult clinical trials in 128 patients with narcolepsy administered immediate-release sodium oxybate, two subjects had profound CNS depression, which resolved after supportive respiratory intervention. Two other patients discontinued immediate-release sodium oxybate because of severe difficulty breathing and an increase in obstructive sleep apnea. In two controlled trials assessing polysomnographic (PSG) measures in adult patients with narcolepsy administered immediate-release sodium oxybate, 40 of 477 patients were included with a baseline apnea/hypopnea index of 16 to 67 events per hour, indicative of mild to severe sleep-disordered breathing. None of the 40 patients had a clinically significant worsening of respiratory function, as measured by apnea/hypopnea index and pulse oximetry at doses of 4.5 g to 9 g per night.

Prescribers should be aware that sleep-related breathing disorders tend to be more prevalent in obese patients, in men, in postmenopausal women not on hormone replacement therapy, and among patients with narcolepsy. Increased central apneas and clinically relevant desaturation events have been observed with immediate-release sodium oxybate administration in adult and pediatric patients.

## **5.5 Depression and Suicidality**

Depression, and suicidal ideation and behavior, can occur in patients treated with LUMRYZ.

In an adult clinical trial in patients with narcolepsy administered LUMRYZ [*see Adverse Reactions (6.1)*], there were no suicide attempts, but one patient developed suicidal ideation at the 9 g dose. In adult clinical trials in patients with narcolepsy (n=781) administered immediate-release sodium oxybate, there were two suicides and two attempted suicides in patients treated with immediate-release sodium oxybate, including three patients with a previous history of depressive psychiatric disorder. Of the two suicides, one patient used immediate-release sodium oxybate in conjunction with other drugs. Immediate-release sodium oxybate was not involved in the second suicide. Adverse reactions of depression were reported by 7% of 781 patients treated with immediate-release sodium oxybate, with four patients (<1%) discontinuing because of depression. In most cases, no change in immediate-release sodium oxybate treatment was required.

In a controlled trial in adults with narcolepsy administered LUMRYZ where patients were titrated from 4.5 g to 9 g per night, the incidences of depression were 0% at 4.5 g, 1% at 6 g, 1.1% at 7.5 g, and 1.3% at 9 g. In a controlled adult trial, with patients randomized to fixed doses of 3 g, 6 g, or 9 g per night immediate-release sodium oxybate or placebo, there was a single event of depression at the 3 g per night dose. In another adult controlled trial, with patients titrated from an initial 4.5 g per night starting dose of immediate-release sodium oxybate, the incidences of depression were 1.7%, 1.5%, 3.2%, and 3.6% for the placebo, 4.5 g, 6 g, and 9 g per night doses, respectively.

In a clinical trial in pediatric patients with narcolepsy (n=104) administered immediate-release sodium oxybate, one patient experienced suicidal ideation and two patients reported depression while taking immediate-release sodium oxybate.

The emergence of depression in patients treated with LUMRYZ requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored carefully for the emergence of depressive symptoms while taking LUMRYZ.

## **5.6 Other Behavioral or Psychiatric Adverse Reactions**

Other behavioral and psychiatric adverse reactions can occur in patients taking LUMRYZ.

During adult clinical trials in patients with narcolepsy administered LUMRYZ, 2% of 107 patients treated with LUMRYZ experienced a confusional state. During adult clinical trials in patients with narcolepsy administered immediate-release sodium oxybate, 3% of 781 patients treated with immediate-release sodium oxybate experienced confusion, with incidence generally increasing with dose.

No patients treated with LUMRYZ discontinued treatment because of confusion. Less than 1% of patients discontinued the immediate-release sodium oxybate because of confusion. Confusion was reported at all recommended doses of immediate-release sodium oxybate from 6 g to 9 g per night. In a controlled trial in adults where patients were randomized to immediate-release sodium oxybate in fixed total daily doses of 3 g, 6 g, or 9 g per night or placebo, a dose-response relationship for confusion was demonstrated, with 17% of patients at 9 g per night experiencing confusion. In that controlled trial, the confusion resolved in all cases soon after termination of treatment. In one trial where immediate-release sodium oxybate was titrated from an initial 4.5 g per night dose, there was a single event of confusion in one patient at the 9 g per night dose. In the majority of cases in all adult clinical trials in patients with narcolepsy administered immediate-release sodium oxybate, confusion resolved either soon after termination of dosing or with continued treatment.

Anxiety occurred in 7.5% of 107 patients treated with LUMRYZ in the adult trial in patients with narcolepsy. Anxiety occurred in 5.8% of the 874 patients receiving immediate-release sodium oxybate in adult clinical trials in another population.

Other psychiatric reactions reported in adult clinical trials in patients with narcolepsy administered LUMRYZ included irritability, emotional disorder, panic attack, agitation, delirium, and obsessive thoughts. Other neuropsychiatric reactions reported in adult clinical trials in patients with narcolepsy administered immediate-release sodium oxybate and in the postmarketing setting for immediate-release sodium oxybate include hallucinations, paranoia, psychosis, aggression, and agitation.

In a clinical trial in pediatric patients with narcolepsy administered immediate-release sodium oxybate, neuropsychiatric reactions, including acute psychosis, confusion, and anxiety were reported while taking immediate-release sodium oxybate.

The emergence or increase in the occurrence of behavioral or psychiatric events in patients taking LUMRYZ should be carefully monitored.

## **5.7 Parasomnias**

Parasomnias can occur in patients taking LUMRYZ.

Sleepwalking, defined as confused behavior occurring at night and at times associated with wandering, was reported in 3% of 107 adult patients with narcolepsy treated with LUMRYZ. No patients treated with LUMRYZ discontinued due to sleepwalking. Sleepwalking was reported in 6% of 781 patients with narcolepsy treated with immediate-release sodium oxybate in adult controlled and long-term open-label studies, with <1% of patients discontinuing due to sleepwalking. In controlled trials, rates of sleepwalking were similar for patients taking placebo

and patients taking immediate-release sodium oxybate. It is unclear if some or all of the reported sleepwalking episodes correspond to true somnambulism, which is a parasomnia occurring during non-REM sleep, or to any other specific medical disorder. Five instances of sleepwalking with potential injury or significant injury were reported during a clinical trial of immediate-release sodium oxybate in patients with narcolepsy.

Parasomnias, including sleepwalking, have been reported in a pediatric clinical trial and in postmarketing experience with immediate-release sodium oxybate. Therefore, episodes of sleepwalking should be fully evaluated, and appropriate interventions considered.

## 5.8 Use in Patients Sensitive to High Sodium Intake

LUMRYZ has a high sodium content. In patients sensitive to sodium intake (e.g., those with heart failure, hypertension, or renal impairment), consider the amount of daily sodium intake in each dose of LUMRYZ. Table 1 provides the approximate sodium content per LUMRYZ dose.

**Table 1: Approximate Sodium Content per Total Nightly Dose of LUMRYZ (g = grams)**

LUMRYZ Dose	Sodium Content/Total Nightly Exposure
4.5 g per night	820 mg
6 g per night	1100 mg
7.5 g per night	1400 mg
9 g per night	1640 mg

## 6 ADVERSE REACTIONS

The following clinically significant adverse reactions appear in other sections of the labeling:

- CNS Depression *[see Warnings and Precautions (5.1)]*
- Abuse and Misuse *[see Warnings and Precautions (5.2)]*
- Respiratory Depression and Sleep-Disordered Breathing *[see Warnings and Precautions (5.4)]*
- Depression and Suicidality *[see Warnings and Precautions (5.5)]*
- Other Behavioral or Psychiatric Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Parasomnias *[see Warnings and Precautions (5.7)]*
- Use in Patients Sensitive to High Sodium Intake *[see Warnings and Precautions (5.8)]*

## 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 rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

### Adult Patients

LUMRYZ was studied in one placebo-controlled trial (Study 1) [see *Clinical Studies (14.1)*] in 212 patients with narcolepsy (107 patients treated with LUMRYZ and 105 with placebo).

### *Adverse Reactions Leading to Treatment Discontinuation*

In Study 1, 15.9% of patients treated with LUMRYZ discontinued because of adverse reactions, compared to 1.9% of patients receiving placebo. The most common adverse reaction leading to discontinuation was dizziness (4.7%). For LUMRYZ, 5.6% of patients discontinued due to adverse reactions on 4.5 g, 4.1% on 6 g, 4.5% on 7.5 g, and 3.9% on 9 g dose.

### *Most Common Adverse Reactions*

The most common adverse reactions (incidence  $\geq 5\%$  and greater than placebo) reported for any dose of LUMRYZ were nausea, dizziness, enuresis, headache, and vomiting.

### *Adverse Reactions Occurring at an Incidence of 2% or Greater*

Table 2 lists adverse reactions occurring in 2% or more of LUMRYZ-treated patients on any individual dose and at a rate greater than placebo-treated patients in Study 1.

**Table 2: Adverse Reactions Occurring in 2% or More of LUMRYZ-Treated Adult Patients and Greater than for Placebo-Treated Patients in Study 1**

Adverse Reaction	Placebo (N=105) %	LUMRYZ 4.5 g (N=107) %	LUMRYZ 6 g (N=97) %	LUMRYZ 7.5 g (N=88) %	LUMRYZ 9 g (N=77) %
<b>Gastrointestinal Disorders</b>					
Vomiting	2	3	3	6	5
Nausea	3	6	8	7	1
<b>Investigations</b>					
Weight Decreased	0	1	0	0	4
<b>Metabolism and Nutritional Disorders</b>					
Decreased Appetite	0	4	4	3	3
<b>Nervous System Disorders</b>					
Dizziness	0	6	4	6	5
Somnolence	1	0	1	2	4
Headache	6	7	5	6	0
<b>Psychiatric Disorders</b>					
Enuresis	0	2	4	9	9
Anxiety	1	3	1	3	1
Somnambulism	0	1	2	0	0

### *Dose-Response Information*

In the clinical trial in adult patients with narcolepsy, a dose-response relationship was observed for enuresis and somnolence.

### *Additional Adverse Reactions*

Adverse reactions observed in clinical studies with immediate-release sodium oxybate ( $\geq 2\%$ ), but not observed in Study 1 at a frequency of higher than 2%, and which may be relevant for LUMRYZ: diarrhea, abdominal pain upper, dry mouth, pain, feeling drunk, peripheral edema, cataplexy, muscle spasms, pain in extremity, tremor, disturbance in attention, paresthesia, sleep paralysis, disorientation, irritability, and hyperhidrosis.

#### Pediatric Patients (7 Years of Age and Older)

The safety of LUMRYZ for the treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy is supported by an adequate and well-controlled trial of immediate-release sodium oxybate [*see Clinical Studies (14.2)*]. Below is a display of adverse reactions of immediate-release sodium oxybate in this adequate and well-controlled trial.

In this trial, 104 patients aged 7 to 17 years (37 patients aged 7 to 11 years; 67 patients aged 12 to 17 years) with narcolepsy received immediate-release sodium oxybate for up to one year. This trial included an open-label safety continuation period in which eligible patients received immediate-release sodium oxybate for up to an additional 2 years. The median and maximum exposure across the entire trial were 371 and 987 days, respectively.

#### *Adverse Reactions Leading to Treatment Discontinuation*

In the pediatric clinical trial with immediate-release sodium oxybate, 7 of 104 patients reported adverse reactions that led to withdrawal from the study (hallucination, tactile; suicidal ideation; weight decreased; sleep apnea syndrome; affect lability; anger, anxiety, depression; and headache).

#### *Adverse Reactions in the Pediatric Clinical Trial*

The most common adverse reactions ( $\geq 5\%$ ) were nausea (20%), enuresis (19%), vomiting (18%), headache (17%), weight decreased (13%), decreased appetite (9%), dizziness (8%), and sleepwalking (6%).

Additional information regarding safety in pediatric patients appears in the following sections:

- Respiratory Depression and Sleep-Disordered Breathing [*see Warnings and Precautions (5.4)*]
- Depression and Suicidality [*see Warnings and Precautions (5.5)*]
- Other Behavioral or Psychiatric Adverse Reactions [*see Warnings and Precautions (5.6)*]
- Parasomnias [*see Warnings and Precautions (5.7)*]

The overall adverse reaction profile of immediate-release sodium oxybate in the pediatric clinical trial was similar to that seen in the adult clinical trial with immediate-release sodium oxybate. The safety profile in pediatric patients with LUMRYZ is expected to be similar to that of adult patients treated with LUMRYZ and to that of pediatric patients treated with immediate-release sodium oxybate.



## 6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of sodium oxybate. 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:

Arthralgia, decreased appetite, fall\*, fluid retention, hangover, headache, hypersensitivity, hypertension, memory impairment, nocturia, panic attack, vision blurred, and weight decreased.

\*The sudden onset of sleep in patients taking sodium oxybate, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization.

## 7 DRUG INTERACTIONS

### 7.1 Alcohol, Sedative Hypnotics, and CNS Depressants

LUMRYZ is contraindicated for use in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of LUMRYZ [*see Warnings and Precautions (5.1)*]. In addition to coadministration of LUMRYZ and alcohol being contraindicated because of respiratory depression, consumption of alcohol while taking LUMRYZ may also result in a more rapid release of the dose of sodium oxybate [*see Clinical Pharmacology (12.3)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

There are no adequate data on the developmental risk associated with the use of sodium oxybate in pregnant women. Oral administration of sodium oxybate to pregnant rats (150, 350, or 1,000 mg/kg/day) or rabbits (300, 600, or 1,200 mg/kg/day) throughout organogenesis produced no clear evidence of developmental toxicity; however, oral administration to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring postnatal viability and growth, at a clinically relevant dose [*see Data*].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

#### Clinical Considerations

##### *Labor or Delivery*

LUMRYZ has not been studied in labor or delivery. In obstetric anesthesia using an injectable formulation of sodium oxybate, newborns had stable cardiovascular and respiratory measures but were very sleepy, causing a slight decrease in Apgar scores. There was a fall in the rate of uterine

contractions 20 minutes after injection. Placental transfer is rapid and gamma-hydroxybutyrate (GHB) has been detected in newborns at delivery after intravenous administration of GHB to mothers. Subsequent effects of sodium oxybate on later growth, development, and maturation in humans are unknown.

## Data

### *Animal Data*

Oral administration of sodium oxybate to pregnant rats (150, 350, or 1,000 mg/kg/day) or rabbits (300, 600, or 1,200 mg/kg/day) throughout organogenesis produced no clear evidence of developmental toxicity. The highest doses tested in rats and rabbits were approximately 1 and 3 times, respectively, the maximum recommended human dose (MRHD) of 9 g per night on a body surface area (mg/m<sup>2</sup>) basis.

Oral administration of sodium oxybate (150, 350, or 1,000 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring postnatal viability and body weight gain at the highest dose tested. The no-effect dose for pre- and postnatal developmental toxicity in rats is less than the MRHD on a mg/m<sup>2</sup> basis.

## **8.2 Lactation**

### Risk Summary

GHB is excreted in human milk after oral administration of sodium oxybate. There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUMRYZ and any potential adverse effects on the breastfed infant from LUMRYZ or from the underlying maternal condition.

## **8.4 Pediatric Use**

LUMRYZ has not been studied in a pediatric clinical trial. The safety and effectiveness of LUMRYZ in the treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy is supported by evidence from a double-blind, placebo-controlled, randomized-withdrawal study of immediate-release sodium oxybate [*see Adverse Reactions (6.1) and Clinical Studies (14.2)*].

In the pediatric clinical trial with immediate-release sodium oxybate administration in pediatric patients 7 years of age and older with narcolepsy, serious adverse reactions of central sleep apnea and oxygen desaturation documented by polysomnography evaluation; depression; suicidal ideation; neuropsychiatric reactions including acute psychosis, confusion, and anxiety; and parasomnias, including sleepwalking, have been reported [*see Warnings and Precautions (5.4, 5.5, 5.6, 5.7) and Adverse Reactions (6.1)*].

The safety and effectiveness of LUMRYZ have not been established in pediatric patients younger than 7 years old.

### Juvenile Animal Toxicity Data

In a study in which sodium oxybate (0, 100, 300, or 900 mg/kg/day) was orally administered to rats during the juvenile period of development (postnatal days 21 through 90), mortality was



observed at the two highest doses tested. Deaths occurred during the first week of dosing and were associated with clinical signs (including decreased activity and respiratory rate) consistent with the pharmacological effects of the drug. Reduced body weight gain in males and females and delayed sexual maturation in males were observed at the highest dose tested. The no-effect dose for adverse effects in juvenile rats is associated with plasma exposures (AUC) less than that at the maximum recommended human dose (9 g/night).

## **8.5 Geriatric Use**

Clinical studies of LUMRYZ or immediate-release sodium oxybate in patients with narcolepsy did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects. In controlled trials of immediate-release sodium oxybate in another population, 39 (5%) of 874 patients were 65 years or older. Discontinuations of treatment due to adverse reactions were increased in the elderly compared to younger adults (21% vs. 19%). Frequency of headaches was markedly increased in the elderly (39% vs. 19%). The most common adverse reactions were similar in both age categories. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

## **8.6 Hepatic Impairment**

Because of an increase in exposure to LUMRYZ, LUMRYZ should not be initiated in patients with hepatic impairment because appropriate dosage adjustments for initiation of LUMRYZ cannot be made with the available dosage strengths [*see Clinical Pharmacology (12.3)*]. Patients with hepatic impairment who have been titrated to a maintenance dosage of another oxybate product can be switched to LUMRYZ if the appropriate dosage strength is available.

# **9 DRUG ABUSE AND DEPENDENCE**

## **9.1 Controlled Substance**

LUMRYZ is a Schedule III controlled substance under the Federal Controlled Substances Act. Non-medical use of LUMRYZ could lead to penalties assessed under the higher Schedule I controls.

## **9.2 Abuse**

LUMRYZ (sodium oxybate), the sodium salt of GHB, produces dose-dependent central nervous system effects, including hypnotic and positive subjective reinforcing effects. The onset of effect is rapid, enhancing its potential for abuse or misuse.

Drug abuse is the intentional non-therapeutic use of a drug product or substance, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed. Drug misuse and abuse may occur with or without progression to addiction. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing

drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

The rapid onset of sedation, coupled with the amnestic features of GHB, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim).

Illicit GHB is abused in social settings primarily by young adults. Some of the doses estimated to be abused are in a similar dosage range to that used for treatment of patients with cataplexy. GHB has some commonalities with ethanol over a limited dose range, and some cross tolerance with ethanol has been reported as well. Cases of severe dependence and craving for GHB have been reported when the drug is taken around the clock. Patterns of abuse indicative of dependence include: 1) the use of increasingly large doses, 2) increased frequency of use, and 3) continued use despite adverse consequences.

Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g., increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy). Dispose of LUMRYZ according to state and federal regulations. It is safe to dispose of LUMRYZ down the sanitary sewer.

### **9.3 Dependence**

#### Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. There have been case reports of withdrawal, ranging from mild to severe, following discontinuation of illicit use of GHB at frequent repeated doses (18 g to 250 g per day) in excess of the recommended dosage range. Signs and symptoms of GHB withdrawal following abrupt discontinuation included insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, tachycardia, headache, dizziness, rebound fatigue and sleepiness, confusion, and, particularly in the case of severe withdrawal, visual hallucinations, agitation, and delirium. These symptoms generally abated in 3 to 14 days. In cases of severe withdrawal, hospitalization may be required. The discontinuation effects of LUMRYZ have not been systematically evaluated in controlled clinical trials. In the clinical trial experience with immediate-release sodium oxybate in narcolepsy/cataplexy patients at recommended doses, two patients reported anxiety and one reported insomnia following abrupt discontinuation at the termination of the clinical trial; in the two patients with anxiety, the frequency of cataplexy had increased markedly at the same time.

#### Tolerance

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Tolerance to LUMRYZ has not been systematically studied in controlled clinical trials. There have been some case reports of symptoms of tolerance developing after illicit use at dosages far in excess of the recommended LUMRYZ dosage regimen. Clinical studies of immediate-release sodium oxybate in the treatment of alcohol

withdrawal suggest a potential cross-tolerance with alcohol. The safety and effectiveness of LUMRYZ in the treatment of alcohol withdrawal have not been established.

## **10 OVERDOSAGE**

### **10.1 Human Experience**

Information regarding overdose with LUMRYZ is derived largely from reports in the medical literature that describe symptoms and signs in individuals who have ingested GHB illicitly. In these circumstances, the co-ingestion of other drugs and alcohol was common and may have influenced the presentation and severity of clinical manifestations of overdose.

In adult clinical trials of immediate-release sodium oxybate, two cases of overdose with sodium oxybate were reported. In the first case, an estimated dose of 150 g, more than 15 times the maximum recommended dose, caused a patient to be unresponsive with brief periods of apnea and to be incontinent of urine and feces. This individual recovered without sequelae. In the second case, death was reported following a multiple drug overdose consisting of sodium oxybate and numerous other drugs.

### **10.2 Signs and Symptoms**

Information about signs and symptoms associated with overdosage with LUMRYZ derives from reports of illicit use of GHB. Patient presentation following overdose is influenced by the dose ingested, the time since ingestion, the co-ingestion of other drugs and alcohol, and the fed or fasted state. Patients have exhibited varying degrees of depressed consciousness that may fluctuate rapidly between a confusional, agitated combative state with ataxia and coma. Emesis (even when obtunded), diaphoresis, headache, and impaired psychomotor skills have been observed. No typical pupillary changes have been described to assist in diagnosis; pupillary reactivity to light is maintained. Blurred vision has been reported. An increasing depth of coma and acidosis have been observed at higher doses. Myoclonus and tonic-clonic seizures have been reported.

Respiration may be unaffected or compromised in rate and depth. Cheyne-Stokes respiration and apnea have been observed. Bradycardia and hypothermia may accompany unconsciousness, as well as muscular hypotonia, but tendon reflexes remain intact.

### **10.3 Recommended Treatment of Overdose**

General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if co-ingestants are suspected. Because emesis may occur in the presence of obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation may be warranted. Although the gag reflex may be absent in deeply comatose patients, even unconscious patients may become combative to intubation, and rapid-sequence induction (without the use of sedative) should be considered. Vital signs and consciousness should be closely monitored. The bradycardia reported with GHB overdose has been responsive to atropine intravenous administration. No reversal of the central depressant effects of LUMRYZ can be expected from naloxone or flumazenil administration. The use of hemodialysis and other forms of extracorporeal drug removal have not been studied in GHB

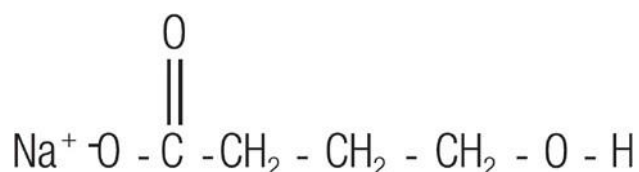
overdose, but have been reported in cases of acidosis associated with GHB ingestions of 125 g or greater; however, due to the rapid metabolism of sodium oxybate, these measures may not be warranted.

## 10.4 Poison Control Center

As with the management of all cases of drug overdosage, the possibility of multiple drug ingestion should be considered. The healthcare provider is encouraged to collect urine and blood samples for routine toxicologic screening, and to consult with a regional poison control center (1-800-222-1222) for current treatment recommendations.

## 11 DESCRIPTION

Sodium oxybate, a CNS depressant, is the active ingredient in LUMRYZ for extended-release oral suspension. The chemical name for sodium oxybate is sodium 4-hydroxybutyrate. The molecular formula is  $C_4H_7NaO_3$ , and the molecular weight is 126.09 g/mole. The chemical structure is:



Sodium oxybate is a white to off-white solid powder.

Each packet of LUMRYZ contains 4.5 g, 6 g, 7.5 g, or 9 g of sodium oxybate, equivalent to 3.7 g, 5.0 g, 6.2 g, or 7.4 g of oxybate, respectively. The inactive ingredients are carrageenan, hydrogenated vegetable oil, hydroxyethyl cellulose, magnesium stearate, malic acid, methacrylic acid copolymer, microcrystalline cellulose, povidone, and xanthan gum.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

LUMRYZ is a CNS depressant. The mechanism of action of LUMRYZ in the treatment of narcolepsy is unknown. Sodium oxybate is the sodium salt of gamma-hydroxybutyrate (GHB), an endogenous compound and metabolite of the neurotransmitter GABA. It is hypothesized that the therapeutic effects of LUMRYZ on cataplexy and excessive daytime sleepiness are mediated through GABA<sub>B</sub> actions at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.

### 12.3 Pharmacokinetics

Following oral administration of LUMRYZ, the plasma levels of GHB increased dose-proportionally for  $C_{max}$  and more than dose-proportionally for area under the plasma

concentration-time curve ( $AUC_{inf}$ ) (respectively, 2-fold and 2.3-fold increases as total daily dose is doubled from 4.5 g to 9 g).

No clinically significant difference in oxybate pharmacokinetics was observed between a single 6 g dose of LUMRYZ and two 3 g doses of immediate-release sodium oxybate administered 4 hours apart.

### Absorption

Following oral administration of a single 6 g dose of LUMRYZ, the peak plasma concentration ( $C_{max}$ ) was 66 mcg/mL and the time to peak plasma concentration ( $T_{max}$ ) was 1.5 hours.

### *Effect of Food*

Administration of LUMRYZ immediately after a high-fat meal resulted in a mean reduction in  $C_{max}$  and AUC of GHB by 33% and 14%, respectively; average  $T_{max}$  increased from 0.5 hours to 1.5 hours [see *Dosage and Administration* (2.3)].

### *Effect of Ethanol*

An in vitro study showed alcohol-induced dose-dumping of sodium oxybate from extended-release oral suspension at 1 hour in the presence of 40% alcohol, and approximately 60% increase of drug release at 2 hours in the presence of 20% alcohol [see *Contraindications* (4) and *Warnings and Precautions* (5.1)].

### *Effect of Water Temperature*

An in vitro dissolution study showed that LUMRYZ mixed with hot water (90°C) resulted in a dose-dumping phenomenon for the release of sodium oxybate, whereas warm water (50°C) did not significantly affect the drug release from the extended-release suspension [see *Dosage and Administration* (2.3)].

### Distribution

GHB is a hydrophilic compound with an apparent volume of distribution averaging 190 mL/kg to 384 mL/kg. At GHB concentrations ranging from 3 mcg/mL to 300 mcg/mL, less than 1% is bound to plasma proteins.

### Elimination

#### *Metabolism*

Animal studies indicate that metabolism is the major elimination pathway for GHB, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle, and secondarily by  $\beta$ -oxidation. The primary pathway involves a cytosolic NADP<sup>+</sup>-linked enzyme, GHB dehydrogenase, which catalyzes the conversion of GHB to succinic semialdehyde, which is then biotransformed to succinic acid by the enzyme succinic semialdehyde dehydrogenase. Succinic acid enters the Krebs cycle where it is metabolized to carbon dioxide and water. A second mitochondrial oxidoreductase enzyme, a transhydrogenase, also catalyzes the conversion to succinic semialdehyde in the presence of  $\alpha$ -ketoglutarate. An alternate pathway of biotransformation involves  $\beta$ -oxidation via 3,4-dihydroxybutyrate to carbon dioxide and water. No active metabolites have been identified.

#### *Excretion*

The clearance of GHB is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. On average, less than 5% of unchanged drug appears in human urine within 6 to 8 hours after dosing. Fecal excretion is negligible. GHB has an elimination half-life of 0.5 to 1 hour.

### Specific Population

#### *Geriatric Patients*

There is limited experience with LUMRYZ in the elderly. Results from a pharmacokinetic study of immediate-release sodium oxybate (n=20) in another studied population indicate that the pharmacokinetic characteristics of GHB are consistent among younger (age 48 to 64 years) and older (age 65 to 75 years) adults.

#### *Pediatric Patients*

The pharmacokinetics of LUMRYZ has not been directly evaluated in pediatric patients.

The pharmacokinetics of immediate-release sodium oxybate were evaluated in pediatric patients 7 to 17 years of age (n=29). The pharmacokinetic characteristics of immediate-release sodium oxybate were shown to be similar in adults and pediatric patients. Body weight was found to be the major intrinsic factor affecting oxybate pharmacokinetics.

#### *Male and Female Patients*

In a study of 18 female and 18 male healthy adult volunteers, no gender differences were detected in the pharmacokinetics of GHB following an immediate-release 4.5 g oral dose of sodium oxybate.

#### *Racial or Ethnic Groups*

There are insufficient data to evaluate any pharmacokinetic differences among races.

#### *Patients with Renal Impairment*

No pharmacokinetic study in patients with renal impairment has been conducted.

#### *Patients with Hepatic Impairment*

The pharmacokinetics of GHB in 16 cirrhotic patients, half without ascites (Child's Class A) and half with ascites (Child's Class C), were compared to the kinetics in 8 subjects with normal hepatic function, after a single sodium oxybate oral dose of 25 mg/kg. AUC values were doubled in cirrhotic patients, with apparent oral clearance reduced from 9.1 mL/min/kg in healthy adults to 4.5 and 4.1 mL/min/kg in Class A and Class C patients, respectively. Elimination half-life was significantly longer in Class C and Class A patients than in control patients (mean  $t_{1/2}$  of 59 minutes and 32 minutes, respectively, versus 22 minutes in control patients). LUMRYZ should not be initiated in patients with liver impairment [see *Use in Specific Populations* (8.6)].

### Drug Interaction Studies

*In vitro* studies with pooled human liver microsomes indicate that sodium oxybate does not significantly inhibit the activities of the human isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A, up to the concentration of 3 mM (378 mcg/mL), a level considerably higher than levels achieved with the maximum recommended dose.



A drug interaction study in healthy adults (age 18 to 55 years) was conducted with LUMRYZ and divalproex sodium. Co-administration of a single dose of LUMRYZ (6 g) with divalproex sodium ER at steady state resulted in an approximate 18% increase in AUC (90% CI ratio range of 112%-123%), which is not expected to be clinically meaningful, while  $C_{max}$  was comparable. A single dose of LUMRYZ (6 g) did not appear to affect the pharmacokinetics of divalproex sodium. However, a pharmacodynamic interaction between LUMRYZ and divalproex sodium, a sedative antiepileptic drug, cannot be ruled out [see *Warnings and Precautions (5.1)* and *Drug Interactions (7.1)*].

Drug interaction studies in healthy adults (age 18 to 50 years) were conducted with immediate-release sodium oxybate and diclofenac and ibuprofen:

- Diclofenac: Co-administration of sodium oxybate (6 g per day as two equal doses of 3 grams dosed four hours apart) with diclofenac (50 mg/dose twice per day) showed no significant changes in systemic exposure to GHB. Co-administration did not appear to affect the pharmacokinetics of diclofenac.
- Ibuprofen: Co-administration of sodium oxybate (6 g per day as two equal doses of 3 grams dosed four hours apart) with ibuprofen (800 mg/dose four times per day also dosed four hours apart) resulted in comparable systemic exposure to GHB, as shown by plasma  $C_{max}$  and AUC values. Co-administration did not affect the pharmacokinetics of ibuprofen.

Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between immediate-release sodium oxybate and protriptyline hydrochloride, zolpidem tartrate, and modafinil. Also, there were no pharmacokinetic interactions with the alcohol dehydrogenase inhibitor fomepizole. However, pharmacodynamic interactions with these drugs cannot be ruled out. Alteration of gastric pH with omeprazole produced no significant change in the pharmacokinetics of GHB. In addition, drug interaction studies in healthy adults demonstrated no pharmacokinetic or clinically significant pharmacodynamic interactions between immediate-release sodium oxybate and duloxetine HCl.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis

Administration of sodium oxybate to rats at oral doses of up to 1,000 mg/kg/day for 83 (males) or 104 (females) weeks resulted in no increase in tumors. Plasma exposure (AUC) at the highest dose tested was 2 times that in humans at the maximum recommended human dose (MRHD) of 9 g per night.

The results of 2-year carcinogenicity studies in mouse and rat with gamma-butyrolactone, a compound that is metabolized to sodium oxybate *in vivo*, showed no clear evidence of carcinogenic activity. The plasma AUCs of sodium oxybate achieved at the highest doses tested in these studies were less than that in humans at the MRHD.

#### Mutagenesis

Sodium oxybate was negative in the *in vitro* bacterial gene mutation assay, an *in vitro* chromosomal aberration assay in mammalian cells, and in an *in vivo* rat micronucleus assay.

#### Impairment of Fertility

Oral administration of sodium oxybate (150, 350, or 1,000 mg/kg/day) to male and female rats prior to and throughout mating and continuing in females through early gestation resulted in no adverse effects on fertility. The highest dose tested is approximately equal to the MRHD on a mg/m<sup>2</sup> basis.

## **14 CLINICAL STUDIES**

### **14.1 Cataplexy and Excessive Daytime Sleepiness (EDS) in Adult Narcolepsy**

The effectiveness of LUMRYZ for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy has been established based on a double-blind, randomized, placebo-controlled, two-arm multi-center study to assess the efficacy and safety of a once nightly administration of LUMRYZ in patients with narcolepsy (Study 1; NCT02720744).

A total of 212 patients were randomized to receive LUMRYZ or placebo in a 1:1 ratio and received at least one dose of study drug. The study was divided into four sequential study periods, and incorporated dose titration to stabilized dose administration of LUMRYZ (4.5 g, 6 g, 7.5 g, and 9 g). There was a three-week screening period, a 13-week treatment period including up-titration over a period of eight weeks, five weeks of stable dosing at 9 g/night, and a one-week follow-up period. Patients could be on concomitant stimulant as long as dosage was stable for 3 weeks prior to study start.

The three co-primary endpoints were the Maintenance of Wakefulness Test (MWT), Clinical Global Impression-Improvement (CGI-I), and mean change in weekly cataplexy attacks. The MWT measures latency to sleep onset (in minutes), averaged over five sessions at 2-hour intervals following nocturnal polysomnography. For each test session, patients were instructed to remain awake for as long as possible during 30-minute test sessions, and sleep latency was determined as the number of minutes patients could remain awake. The overall score was the mean sleep latency for the 5 sessions. The CGI-I was evaluated on a 7-point scale, centered at *No Change*, and ranging from *Very Much Worse* to *Very Much Improved*. Patients were rated by evaluators who based their assessments on the severity of narcolepsy at Baseline.

Demographic and mean baseline characteristics were similar for the LUMRYZ and placebo groups. A total of 76% were narcolepsy type 1 (NT1; with both symptoms of EDS and cataplexy) patients, and 24% were narcolepsy type 2 (NT2; with symptoms of EDS and without cataplexy) patients. The mean age was 31 years, and 68% were female. Approximately 63% of patients were on concomitant stimulant use. The mean MWT at baseline was 5 minutes for the LUMRYZ group, and 4.7 minutes for the placebo group. The mean number of cataplexy attacks per week at baseline was 18.9 in the LUMRYZ group and 19.8 in the placebo group. A statistically significant improvement was seen on the MWT, CGI-I, and mean weekly cataplexy attacks, for the 6 g (Week 3), 7.5 g (Week 8), and 9 g (Week 13) dose of LUMRYZ, compared to the placebo group (see Table 3, Table 4, and Table 5).



**Table 3: Change from Baseline in the Maintenance of Wakefulness Test**

<b>Dose</b>	<b>Treatment Group (N)</b>	<b>Change from Baseline (Minutes)*</b>	<b>Difference from Placebo [95% CI]</b>	<b>p-value</b>
6 g (Week 3)	LUMRYZ (87)	8.1	5.0 [2.90;7.05]	<0.001
	Placebo (88)	3.1	-	-
7.5 g (Week 8)	LUMRYZ (76)	9.6	6.2 [3.84;8.58]	<0.001
	Placebo (78)	3.3	-	-
9 g (Week 13)	LUMRYZ (68)	10.8	6.1 [3.52;8.75]	<0.001
	Placebo (78)	4.7	-	-

\*Mean MWT at baseline was 5.0 minutes for the LUMRYZ group and 4.7 minutes for the placebo group

**Table 4: Proportion of Patients with a Very Much or Much Improved Clinical Global Impression-Improvement**

<b>Dose</b>	<b>Treatment Group (N)</b>	<b>Percentage of Responders (Much or Very Much Improved)</b>	<b>Odds Ratio [95% CI]</b>	<b>p-value</b>
6 g (Week 3)	LUMRYZ (87)	40	10.3 [3.93;26.92]	<0.001
	Placebo (87)	6	-	-
7.5 g (Week 8)	LUMRYZ (75)	64	5.7 [2.82;11.40]	<0.001
	Placebo (81)	22	-	-
9 g (Week 13)	LUMRYZ (69)	73	5.6 [2.76;11.23]	<0.001
	Placebo (79)	32	-	-

**Table 5: Change from Baseline in the Mean Cataplexy Attacks Per Week in NT1 Patients**

<b>Dose</b>	<b>Treatment Group (N)</b>	<b>Change from Baseline*</b>	<b>Difference from Placebo [95% CI]</b>	<b>p-value</b>
6 g (Week 3)	LUMRYZ (73)	-7.4	-4.8 [-7.03;-2.62]	<0.001
	Placebo (72)	-2.6	-	-
7.5 g (Week 8)	LUMRYZ (66)	-10.0	-6.3 [-8.74;-3.80]	<0.001
	Placebo (69)	-3.7	-	-

Dose	Treatment Group (N)	Change from Baseline*	Difference from Placebo [95% CI]	p-value
9 g (Week 13)	LUMRYZ (55)	-11.5	-6.7 [-9.32;-3.98]	<0.001
	Placebo (62)	-4.9	-	-

\*Mean (SD) number of cataplexy attacks per week at baseline was 18.9 (8.7) in the LUMRYZ group and 19.8 (8.9) in the placebo group

## 14.2 Cataplexy and Excessive Daytime Sleepiness (EDS) in Pediatric Narcolepsy

The effectiveness of LUMRYZ in pediatric patients is based upon a clinical study in patients treated with immediate-release sodium oxybate, as described below.

The effectiveness of immediate-release sodium oxybate in the treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy was established in a double-blind, placebo-controlled, randomized-withdrawal study (NCT02221869). The study was conducted in 106 pediatric patients (median age: 12 years; range: 7 to 17 years) with a baseline history of at least 14 cataplexy attacks in a typical 2-week period prior to any treatment for narcolepsy symptoms. Of the 106 patients, 2 did not receive study drug and 63 patients were randomized 1:1 either to continued treatment with immediate-release sodium oxybate or to placebo. Randomization to placebo was stopped early as the efficacy criterion was met at the pre-planned interim analysis.

Patients entered the study either taking a stable dosage of immediate-release sodium oxybate or were immediate-release sodium oxybate-naïve. CNS stimulants were allowed at entry, and approximately 50% of patients continued taking a stable dose of stimulant throughout the stable-dose and double-blind periods. Immediate-release sodium oxybate-naïve patients were initiated and titrated based on body weight over a period of up to 10 weeks. The total nightly dose was administered in two divided doses, with the first dose given at nighttime and the second given 2.5 to 4 hours later. Once a stable dosage of immediate-release sodium oxybate had been achieved, these patients entered the 2-week stable-dose period; patients on a stable dosage of immediate-release sodium oxybate at study entry remained on this dosage for 3 weeks prior to randomization. Efficacy was established at dosages ranging from 3 g to 9 g of immediate-release sodium oxybate per night.

The primary efficacy measure was the change in frequency of cataplexy attacks. In addition, change in cataplexy severity was evaluated with the Clinical Global Impression of Change for cataplexy severity. The Clinical Global Impression of Change is evaluated on a 7-point scale, centered at No Change, and ranging from Very Much Worse to Very Much Improved. The efficacy of immediate-release sodium oxybate in the treatment of excessive daytime sleepiness in pediatric patients with narcolepsy was evaluated with the change in the Epworth Sleepiness Scale (Child and Adolescent) score. The Epworth Sleepiness Scale (Child and Adolescent) is a modified version of the Epworth Sleepiness Scale used in the adult clinical trial with immediate-release sodium oxybate. The Epworth Sleepiness Scale is intended to evaluate the extent of sleepiness in everyday situations by asking the patient a series of questions. In these questions, patients were asked to rate their chances of dozing during each of 8 activities on a scale from 0-3 (0=never; 1=slight; 2=moderate; 3=high). Higher total scores indicate a greater tendency to

sleepiness. The overall change in narcolepsy condition was assessed by the Clinical Global Impression of Change for narcolepsy overall. Efficacy was assessed during or at the end of the 2-week double-blind treatment period, relative to the last 2 weeks or end of the stable-dose period (see Tables 6 and 7).

Pediatric patients taking stable dosages of immediate-release sodium oxybate who were withdrawn from immediate-release sodium oxybate treatment and were randomized to placebo during the double-blind treatment period experienced a statistically significant increase in weekly cataplexy attacks compared with patients who were randomized to continue treatment with immediate-release sodium oxybate. Patients randomized to receive placebo during the double-blind treatment period experienced a statistically significant worsening of EDS compared with patients randomized to continue receiving immediate-release sodium oxybate (see Table 6).

**Table 6: Number of Weekly Cataplexy Attacks and Epworth Sleepiness Scale (Child and Adolescent) Score**

<b>Treatment Group</b>	<b>Baseline<sup>*,†</sup></b>	<b>Double-blind Treatment Period<sup>‡,§</sup></b>	<b>Median Change from Baseline</b>	<b>Comparison to Placebo (p-value<sup>¶</sup>)</b>
<b>Median Number of Cataplexy Attacks (attacks/week)</b>				
Placebo (n=32)	4.7	21.3	12.7	-
Immediate-release Sodium Oxybate (n=31)	3.5	3.8	0.3	<0.0001
<b>Median Epworth Sleepiness Scale (Child and Adolescent) Score</b>				
Placebo (n=31 <sup>**</sup> )	11	12	3	-
Immediate-release Sodium Oxybate (n=30 <sup>**</sup> )	8	9	0	0.0004

\* For weekly number of cataplexy attacks, baseline value is calculated from the last 14 days of the stable-dose period.

† For Epworth Sleepiness Scale score, baseline value is collected at the end of stable-dose period.

‡ Weekly number of cataplexy attacks is calculated from all days within the double-blind treatment period.

§ For Epworth Sleepiness Scale, value is collected at the end of the double-blind treatment period.

¶ P-value from rank-based analysis of covariance (ANCOVA) with treatment as a factor and rank baseline value as a covariate.

\*\* One patient in each of the treatment groups did not have baseline ESS score available and were not included in this analysis.

Patients randomized to receive placebo during the double-blind treatment period experienced a statistically significant worsening of cataplexy severity and narcolepsy overall according to the clinician's assessment compared with patients randomized to continue receiving immediate-release sodium oxybate (see Table 7).

**Table 7: Clinical Global Impression of Change (CGIc) for Cataplexy Severity and Narcolepsy Overall**

<b>Worsened, %<sup>†</sup></b>	<b>CGIc Cataplexy Severity<sup>*</sup></b>	<b>CGIc Narcolepsy Overall<sup>*</sup></b>
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	Placebo (n=32)	Immediate-release Sodium Oxybate (n=29) <sup>‡</sup>	Placebo (n=32)	Immediate-release Sodium Oxybate (n=29) <sup>‡</sup>
<b>Much worse or very much worse</b>	66%	17%	59%	10%
<b>p-value<sup>§</sup></b>	0.0001		<0.0001	

\* Responses indicate change of severity or symptoms relative to receiving immediate-release sodium oxybate treatment at baseline.

† Percentages based on total number of observed values.

‡ Two patients randomized to immediate-release sodium oxybate did not have the CGIC assessments completed and were excluded from the analysis.

§ P-value from Pearson's chi-square test.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

LUMRYZ is a blend of white to off-white granules for extended-release oral suspension in water. LUMRYZ is supplied in cartons and a 28-day starter pack.

*Cartons:* each carton contains either 7 or 30 packets of LUMRYZ, a mixing cup, Prescribing Information and Medication Guide, and Instructions for Use (see Table 8). Dose packets contain a single dose of LUMRYZ provided in 4.5 g, 6 g, 7.5 g, or 9 g doses.

**Table 8: LUMRYZ Carton Configurations**

Strength	Package Size	NDC Number
4.5 g	7 packets	NDC 13551-001-07
	30 packets	NDC 13551-001-30
6 g	7 packets	NDC 13551-002-07
	30 packets	NDC 13551-002-30
7.5 g	7 packets	NDC 13551-003-07
	30 packets	NDC 13551-003-30
9 g	7 packets	NDC 13551-004-07
	30 packets	NDC 13551-004-30

*28-day Starter Pack*: contains four 7-count cartons, each containing a mixing cup, Prescribing Information and Medication Guide, and Instructions for Use (see Table 9). Dose packets contain a single dose of LUMRYZ provided in 4.5 g, 6 g, or 7.5 g doses.

**Table 9: LUMRYZ Starter Pack Contents**

<b>28-day Starter Pack</b>	<b>Strength</b>	<b>Package Size</b>	<b>NDC Number</b>
Week 1	4.5 g	7 packets	NDC 13551-005-01
Week 2	6 g	7 packets	
Week 3	6 g	7 packets	
Week 4	7.5 g	7 packets	

## 16.2 Storage

**Keep out of reach of children.**

LUMRYZ should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature).

Suspensions should be consumed within 30 minutes.

## 16.3 Handling and Disposal

LUMRYZ is a Schedule III drug under the Controlled Substances Act. LUMRYZ should be handled according to state and federal regulations. It is safe to dispose of LUMRYZ down the sanitary sewer.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

### Central Nervous System Depression

Inform patients and/or caregivers that LUMRYZ can cause central nervous system depression, including respiratory depression, hypotension, profound sedation, syncope, and death. Instruct patients to not engage in activities requiring mental alertness or motor coordination, including operating hazardous machinery, for at least 6 hours after taking LUMRYZ. Instruct patients and/or caregivers to inform their healthcare providers of all the medications they take [*see Warnings and Precautions (5.1)*].

### Abuse and Misuse

Inform patients and/or caregivers that the active ingredient of LUMRYZ is gamma-hydroxybutyrate (GHB), which is associated with serious adverse reactions with illicit use and abuse [*see Warnings and Precautions (5.2)*].

### LUMRYZ REMS

LUMRYZ is available only through a restricted program called the LUMRYZ REMS [see *Warnings and Precautions (5.3)*]. Inform the patient and/or caregiver of the following notable requirements:

- LUMRYZ is dispensed only by pharmacies that are specially certified
- LUMRYZ will be dispensed and shipped only to patients who are enrolled in the LUMRYZ REMS

LUMRYZ is available only from certified pharmacies participating in the program. Therefore, provide patients and/or caregivers with the telephone number and website for information on how to obtain the product.

#### Alcohol or Sedative Hypnotics

Advise patients and/or caregivers that alcohol and other sedative hypnotics should not be taken with LUMRYZ [see *Contraindications (4)* and *Warnings and Precautions (5.1)*].

#### Sedation

Inform patients and/or caregivers that they are likely to fall asleep quickly after taking LUMRYZ (often within 5 and usually within 15 minutes), but the time it takes to fall asleep can vary from night to night. The sudden onset of sleep, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization [see *Adverse Reactions (6.2)*]. Instruct patients and/or caregivers that they should remain in bed following ingestion of their dose [see *Dosage and Administration (2.3)*].

#### Food Effects on LUMRYZ

Inform patients and/or caregivers that LUMRYZ should be taken at least 2 hours after eating.

#### Respiratory Depression and Sleep-Disordered Breathing

Inform patients and/or caregivers that LUMRYZ may impair respiratory drive, especially in patients with compromised respiratory function, and may cause apnea [see *Warnings and Precautions (5.4)*].

#### Depression and Suicidality

Instruct patients and/or caregivers to contact a healthcare provider immediately if they develop depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or suicidal ideation [see *Warnings and Precautions (5.5)*].

#### Other Behavioral or Psychiatric Adverse Reactions

Inform patients and/or caregivers that LUMRYZ can cause behavioral or psychiatric adverse reactions, including confusion, anxiety, and psychosis. Instruct them to notify their healthcare provider if any of these types of symptoms occur [see *Warnings and Precautions (5.6)*].

#### Sleepwalking

Instruct patients and/or caregivers that LUMRYZ has been associated with sleepwalking and other behaviors during sleep, and to contact their healthcare provider if this occurs [*see Warnings and Precautions (5.7)*].

Sodium Intake

Instruct patients and/or caregivers that LUMRYZ contains a significant amount of sodium and patients who are sensitive to sodium intake (e.g., those with heart failure, hypertension, or renal impairment) should limit their sodium intake [*see Warnings and Precautions (5.8)*].

**Distributed By:**

Avadel CNS Pharmaceuticals, LLC  
Chesterfield, MO

Protected by U.S. Patent No. D1,032,378

**EXHIBIT C**  
**REDACTED IN**  
**ITS ENTIRETY**



**CERTIFICATE OF SERVICE**

I hereby certify that on June 17, 2025, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on June 17, 2025, upon the following in the manner indicated:

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