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Daridorexant for Insomnia

By: Rachel Larmer, Pharm.D., MBA

Background: Insomnia is defined as difficulty initiating and/or maintaining sleep.[1] It can be classified as chronic, occurring at least three times per week for at least 3 months, or short-term, occurring for less than 3 months. Lack of sufficient sleep can result in daytime symptoms such as fatigue, loss of productivity, decreased functioning, and reduced cognition.[1-3] Insomnia is usually precipitated by a significant stressor (e.g., unemployment/socioeconomic issues, loss of spouse, marital issues) and occurs twice as frequently in females than males. It is estimated that 40% of those with insomnia also have concurrent psychiatric issues (e.g., anxiety, depression, substance abuse disorder).[2-3] Many patients turn to pharmacologic therapy for relief when first-line cognitive behavioral therapy is not possible or ineffective. However hypnotic sedative agents are often associated with with safety issues (e.g., increased risk of falls) and potential for dependency. One newer class of hypnotic medications is the dual orexin receptor antagonists (ORAs), which include suvorexant (Belsomra®; Merck Sharp & Dohme) and lemborexant (Dayvigo®; Eisai, Inc.). Daridorexant (Quviviq®; Idorsia Pharmaceuticals) is the newest ORA and was approved by the Food and Drug Administration (FDA) in January 2022 for insomnia characterized by difficulties with sleep onset and/or sleep maintenance.[4-5] Daridorexant has more favorable pharmacokinetics than other ORA medications and may lead to less daytime somnolence.[6] The half-life of daridorexant is 8 hours compared to suvorexant at 12 hours and lemborexant at 17 to 19 hours.[4,7-8] Of note, like other medications in the ORA class, daridorexant is a Schedule IV Controlled Substance.

Mechanism of Action: Daridorexant exerts its pharmacologic effect through orexin receptor antagonism.[4] Orexin A and B are wake-promoting neuropeptides that bind to the receptors OX1R and OX2R. By blocking this binding, the stimulation to wake up is suppressed and the patient can experience uninterrupted sleep.

Clinical Trials: Two multicenter, randomized, double-blind, placebo-controlled, phase III trials (referred to as Study 1 and Study 2) evaluated the safety and efficacy of daridorexant.[6] In Study 1, patients (N=930) were randomized 1:1:1 to receive daridorexant 50 mg (n=310), daridorexant 25 mg (n=310) or placebo (n=310) for 3 months. In Study 2, patients (N=924) were randomized to receive daridorexant 25 mg (n=309), daridorexant 10 mg (n=307), or placebo (n=308) for 3 months. The trials included a screening period of 7 to 18 days, a single-blind placebo run-in period of 13 to 24 days, a double-blind treatment period of 3 months, and a single-blind placebo run-out period of 7 days followed by a safety follow-up period of 23 days or participation in a 9-month placebo-

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controlled extension study. Adult patients (≥18 years of age) with moderate-to-severe chronic insomnia were enrolled. Randomization was stratified by age <65 or ≥65 years old**.** The primary endpoints were change from baseline in wake time after sleep onset (WASO) and latency to persistent sleep (LPS) at months 1 and 3 (objectively measured by polysomnography). Secondary endpoints included change from baseline in self-reported total sleep time (sTST) and the Insomnia Daytime Symptoms and Impacts Questionnaire sleepiness domain score (IDSIQs) (reported subjectively using an e-diary) at months 1 and 3. Patient characteristics were similar between groups, and most patients were female (67% in Study 1), aged less than 65 years old (61% in Study 1), and white (89% for both studies). Only the results of Study 1 will be covered, since no significant differences were found with the 10 mg dose, which was not FDA-approved. Study 1 showed a significant improvement in WASO and LPS at months 1 and 3 in the 50 mg and 25 mg groups. There was also a significant increase in sTST at months 1 and 3 in both the 50 mg and 25 mg groups. The IDSIQs only improved significantly in the 50 mg group. Select numeric results of these endpoints are listed in Table 1. The authors concluded that both daridorexant 25 mg and 50 mg were safe and effective for sleep induction and maintenance and that the 50 mg dose improved daytime functioning.

Table 1: Select Results from Study 1[6]

	Daridorexant 50 mg	Daridorexant 25 mg
WASO month 1	-22.8 minutes* 95% CI[-28.0 to -17.6] p<0.0001	-12.2 minutes* 95% CI[-17.4 to -7.0] p<0.0001
WASO month 3	-18.3 minutes* 95% CI[-23.9 to -12.7] p<0.0001	-11.9 minutes* 95% CI[-17.5 to -6.2] p<0.0001
LPS month 1	-11.4 minutes* 95% CI[-16.0 to -6.7] p<0.0001	-8.3 minutes* 95% CI[-13.0 to -3.6] p=0.0005
LPS month 3	-11.7 minutes* 95% CI[-16.3 to -7.0] p<0.0001	-7.6 minutes* 95% CI[-12.3 to -2.9] p=0.0015
sTST month 1	22.1 minutes* 95% CI[14.4 to 29.7] p<0.0001	12.6 minutes* 95% CI[5.0 to 20.3] p=0.0013
sTST month 3	19.8 minutes* 95% CI[10.6 to 28.9] p<0.0001	9.9 minutes* 95% CI[0.8 to 19.1] p=0.033
IDSIQs month 1	-1.8* 95% CI[-2.5 to -1.0] p<0.0001	-0.8* 95% CI[-1.5 to 0.01] p=0.055
IDSIQs month 3	-1.9* 95% CI[-2.9 to -0.9] p=0.0002	-1.0* 95% CI[-2.0 to 0.01] p=0.053

***Least means square difference compared with placebo**
CI=Confidence interval WASO=Wake time after sleep onset LPS=Latency to persistent sleep
sTST=Self-reported total sleep time
IDSIQs=Insomnia Daytime Symptoms and Impacts Questionnaire sleepiness domain score

Safety: In phase III clinical trials, the most common adverse reactions that occurred at a frequency ≥ 5% included headache, somnolence, and fatigue.[4]

Dosing and Administration: The recommended dose of daridorexant is 25 mg to 50 mg once daily within 30 minutes of bedtime and at least 7 hours before the planned awakening time.[4-5] The ORA class is generally intended for short-term use of ≤4 to 8 weeks. There are no dosage adjustments necessary for patients with renal impairment. However, the maximum dose is 25 mg/day in patients with moderate hepatic impairment (Child-Pugh class B). Daridorexant is not recommended in cases of severe hepatic impairment (Child-Pugh class C). Since daridorexant is a major substrate of cytochrome P450 (CYP) 3A4, administration with moderate or strong CYP3A4 inducers and strong CYP3A inhibitors should be avoided. Furthermore, the dose should not exceed 25 mg during concurrent therapy with a moderate CYP3A4 inhibitor.

Cost and Availability: Daridorexant is currently available in both 25 mg (NDC 80491-7825-30) and 50 mg (80491-7850-30) tablets in 30-count bottles.[4] The average wholesale price for one tablet of either strength is $18.28.[5] The estimated cost of therapy for 30 days at standard dosing is $548.40.

Formulary Status: Daridorexant is not currently on the CCHS formulary.

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Copanlisib (Aliqopa®) Injection	Antineoplastic Agent	Relapsed Follicular Lymphoma	Restricted to the Department of Hematology/Oncology for outpatient use only
Etoposide Phosphate (Etopophos®) Injection	Antineoplastic Agent	Refractory Testicular Cancer Small Cell Lung Cancer	Restricted to the Department of Hematology/Oncology for use in patients who are unable to tolerate etoposide
Fenfluramine (Fintepla®) Oral Solution	Antiepileptic Agent	Dravet Syndrome Lennox-Gastaut Syndrome	Restricted as follows: 1. For initiation of therapy, it is restricted to the Departments of Epilepsy and Neurology. The prescriber must be enrolled in the Fintepla® REMS program. 2. For continuation of therapy, the inpatient provider does not need to be REMS certified, but the patient still must be enrolled in the Fintepla® REMS program and meet the Fintepla® REMS Program requirements.
Risankizumab (Skyrizi®) Injection	Monoclonal Antibody	Moderate-to-Severe Crohn's Disease	Restricted to the Department of Gastroenterology for outpatient use only
Tralokinumab (Adbry®) Injection	Monoclonal Antibody	Moderate-to-Severe Atopic Dermatitis	Restricted to the Department of Dermatology for outpatient use only in patients whose atopic dermatitis is not adequately controlled with topical prescription therapies (e.g., corticosteroids)

REMS=Risk evaluation mitigation strategy

Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Venetoclax (Venclexta®) Tablets	Antineoplastic Agent	AML	Restricted to the Department of Hematology/Oncology for inpatients if all of the following criteria are met: 1. Emergent new start chemotherapy (new diagnosis or new relapse; not planned chemotherapy admissions) 2. Diagnosis of AML 3. Cycle one of combination with HMA or LDAC 4. Deemed to be unfit or clinically unstable to start treatment in the outpatient setting 5. Unable to obtain venetoclax home supply within 48 hours of the prescription being sent
Vultrisiran (Amvuttra®) Subcutaneous Injection	Anti-Transthyretin Small Interfering Ribonucleic Acid Agent	Polyneuropathy Of Hereditary Transthyretin-Mediated Amyloidosis	Restricted to the Departments of Neurology, Cardiology, and Hematology/ Oncology for outpatient use only

AML=Acute myeloid leukemia HMA=Hypomethylating agent LDAC=Low-dose cytarabine

Product Standardization and Process Changes on Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Pemetrexed (Alimta®) Injection	Antineoplastic Agent	Various Cancers	We will be converting to generic pemetrexed injection from Baxter. It is AB-rated to Alimta®. Conversion to the generic is estimated to yield a considerable cost-savings for the health system
Phenobarbital and Pentobarbital Injections	Barbiturates	Various Neurological Disorders	It is recommended to allow dose rounding for IV phenobarbital and pentobarbital LDs for ease of compounding, administration , and to reduce waste. IV phenobarbital LDs will be rounded to the nearest 65 mg (<32.5 mg round down, ≥32.5 mg round up) IV pentobarbital LDs will be rounded to the nearest 50 mg (<25 mg round down, ≥25 mg round up)

IV=Intravenous LDs=Loading doses

Changes to Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions/ Comments**
Brentuximab vedotin (Adcetris®) Injection	Monoclonal Antibody	Advanced Stage Hodgkin Lymphoma	Modified restrictions to the Department of Hematology/ Oncology for inpatient use in newly diagnosed advanced stage Hodgkin lymphoma
Cidofovir Intralesional Injection	Antiviral Agent	RRP	Modified restrictions to include intralesional use by the Department of Otolaryngology for RRP
Complement inhibitors (ravulizumab, eculizumab, sutimlimab)	Complement Inhibitors	aHUS Myasthenia Gravis PMH	Modified restrictions to remove verbiage: "Agents that may be used as parenteral chemotherapy or biotherapy require order entry by a Staff Physician. Includes initial dose, continuations, discontinuations, and modifications." from the current restriction criteria. **Even though these agents are no longer classified as chemotherapy or biotherapy they still require entry by Staff Physicians.**
COVID-19 Therapies	Antiviral Agents	COVID-19 Treatment	Modified restrictions to align with the definition for high-risk patients for all COVID-19 therapies currently on the CCHS Formulary (oral antivirals, remdesivir and monoclonal antibodies)*
Dalbavancin (Dalvance®) Injection	Glycopeptide	Skin and Soft Tissue Infection	Modified restrictions to include Florida Region Hospital-at-Home with Infectious Diseases consult
Dronedarone (Multaq®) Tablet	Antiarrhythmic Agent	Paroxysmal or Persistent Atrial Fibrillation	Modified restrictions to state: Dronedarone is restricted to Cardiology for initiation of therapy, but there is no restriction for continuation of therapy. Note: A hard stop will be added in Epic on the dronedarone record for prescribers if they answer "yes" to "Does patient have NYHA Class IV heart failure or NYHA Class II-III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic?" After the hard stop, the prescriber must contact a pharmacist to continue with the order.

*Details are in Lexicomp regarding the definition of high-risk patients

RRP=Recurrent respiratory papillomatosis aHUS=Atypical hemolytic uremic syndrome PMH=Paroxysmal nocturnal hemoglobinuria COVID-19=Coronavirus disease 2019 NYHA=New York Heart Association

Changes to Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions/ Comments**
Doxorubicin-Drug-Eluting Beads (DEB)	Antineoplastic Agent	Localized Hepatocellular Carcinoma	Modified restrictions to allow Interventional Radiologists to apply and sign Beacon orders for doxorubicin drug-eluting beads
Mitomycin-C (Mutamycin®) Topical Injection	Antineoplastic Agent	Subglottic and Tracheal Stenosis	Modified restrictions to include topical use by Staff Otolaryngology/ENT for subglottic or tracheal stenosis
Molnupiravir (Lagevrio®) Tablet Nirmatrelavir-Ritonavir (Paxlovid™) Tablet	Antiviral Agent	COVID-19 Treatment	Modified restrictions to include: Inpatients meeting ALL of the following: 1. Positive SARS CoV-2 viral test (PCR or antigen test) and symptoms for < 5 days 2. Not requiring hospitalization at any time for management of COVID-19 3. Not requiring supplemental oxygen or change in baseline supplemental oxygen 4. Mild to moderate COVID-19 infection meeting CCHS high risk criteria for progression to severe COVID-19
Ravulizumab (Ultomiris®) Injection	Monoclonal Antibody	PNH aHUS gMG	Modified restrictions to include REMS-certified staff in the Department of Neurology (Neuromuscular) for outpatient use in patients with refractory gMG positive for anti-acetylcholine receptor antibodies
Tenofovir Alafenamide (Vemlidy®) Tablet	Antiviral Agent	Hepatitis B and HIV treatment of prophylaxis	Removed all restrictions
Tigecycline (Tygacil®) Injection	Antibiotic	Infections due to MDR Gram-Negative Organisms	Modified restrictions as follows: Restricted to the Department of Infectious Diseases
Tranexamic Acid (Lysteda®) Tablet	Antifibrinolytic Agent	Heavy menstrual bleeding Uterine bleeding	Modified restrictions to include Emergency Institute Providers

ENT=Ears nose and throat COVID-19=Coronavirus disease 2019 SARS CoV2=Severe acute respiratory syndrome coronavirus 2
PCR=Polymerase chain reaction PNH=Paroxysmal nocturnal aHUS= Atypical hemolytic uremic syndrome
gMG =Generalized myasthenia gravis HIV=Human immunodeficiency syndrome MDR=Multidrug resistant

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Agalsidase Beta (Fabrazyme®) Injection	Enzyme	Fabry Disease	Restricted to the Departments of Clinical Genetics and Pediatric Hematology/Oncology for outpatient use only

Changes to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions/ Comments**
Dalbavancin (Dalvance®) Injection	Glycopeptide	Skin and Soft Tissue Infection	Modified restrictions to include Florida Region Hospital-at-Home with Infectious Diseases consult
Ferric Carboxymaltose (Injectafer®) Injection	Iron Preparation	Iron deficiency Anemia	Modified restrictions as follows: Restricted to outpatient use only for the treatment of iron deficiency or iron deficiency anemia in patients aged 1 year and older who have an intolerance to or poor response to oral iron
Infliximab (Remicade®) Injection	Monoclonal Antibody	IBD	Modified restriction to include the Staff physicians from the Department of Pediatric Gastroenterology for inpatient use based specific criteria*
Nirmatrelavir-Ritonavir (Paxlovid™) Tablet	Antiviral Agent	COVID-19 Treatment	Modified restrictions to include: Inpatients meeting ALL of the following: 1. Positive SARS CoV-2 viral test (PCR or antigen test) and symptoms for < 5 days 2. Not requiring hospitalization at any time for management of COVI-19 3. Not requiring supplemental oxygen or change in baseline supplemental oxygen 4. Mild to moderate COVID-19 infection meeting CCHS high risk criteria for progression to severe COVID-19
Tigecycline (Tygacil®) Injection	Antibiotic	Infections due to MDR Gram-Negative Organisms	Modified restrictions as follows: Restricted to the Department of Pediatric Infectious Diseases

*Details in Lexicomp
IBD=Inflammatory bowel disease COVID-19=Coronavirus disease 2019 SARS CoV-2=Severe acute respiratory syndrome coronavirus 2
PCR=Polymerase chain reaction MDR=Multidrug resistant