Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Drug Use Evaluation: Modafinil/Armodafinil Safety

Research Questions:

1. Is modafinil or armodafinil therapy associated with increased risk of harm based on medical claims data in the adult Oregon Medicaid population?
2. How frequently is modafinil or armodafinil therapy prescribed to women during pregnancy or in women of child-bearing age who do not have evidence of birth control?
3. What proportion of patients have a mental health comorbidity (psychosis, depression, or mania) which may put them at increased risk of adverse events with modafinil or armodafinil therapy?
4. How frequently do patients prescribed modafinil or armodafinil in the Oregon Medicaid adult population have hospitalizations or emergency department visits for adverse drug events?

Conclusions:

- Modafinil and/or armodafinil adverse events that resulted in recent European Medicines Agency (EMU), Heath Canada and/or FDA labeling changes were: risk of congenital malformations including cardiac anomalies, reproductive toxicity, serious dermatologic reactions, angioedema and anaphylactic reactions, drug rash with eosinophilia and systemic symptoms (DRESS), suicidal ideation, and psychiatric adverse reactions some of which have resulted in hospitalization.
- In 2018-2019, less than 2% of Oregon Medicaid adult females ages 18-39 had claims indicating they were pregnant in the 3 months after modafinil/armodafinil treatment initiation.
- Over three-quarters (77%) of female patients ages 18-39 prescribed continuous modafinil/armodafinil therapy did not have evidence of claims for a contraceptive agent (diaphragms, condoms, nonoxynol 9/spermicide, or oral contraceptives) up to 4 months before and up to 4 months after starting therapy. Other contraceptive products either not obtained at pharmacy point of sale or non-prescription contraceptive mechanisms were not captured in the claims data. Given the documented drug interaction with modafinil/armodafinil and hormonal contraception, alternative methods of birth control may have been more common in this population.
- Overall, roughly 18% of patients had ER visit claims and 2.4% had a hospitalization up to 3 months after modafinil/armodafinil therapy initiation which were similar rates to ER/hospitalizations within 90 days prior to starting modafinil/armodafinil. Over three quarters (77%) of new-start patients had at least 1 high-risk comorbidity present prior to therapy initiation including cardiovascular disease (29%), psychosis (5%), anxiety disorders (42%), and/or mood disorders (62%). Subgroup analysis by comorbidity revealed that in those with preexisting cardiovascular disease, there was a 10% increase in ER visits in the 3 months after therapy initiation compared to the 3 months before.
- The most common adverse event reported up to 30 days after modafinil/armodafinil therapy initiation were psychiatric (29%) and cardiovascular (2%) symptoms.

Author: David Engen, PharmD

October 2020

- Within 6 months of modafinil/armodafinil initiation, roughly 9% of individuals had new psychiatric symptoms and 3-4% of patients had new cardiovascular symptoms with no prior history of claims for a similar diagnosis.

Recommendations:

- Modify modafinil/armodafinil prior authorization criteria to prevent inappropriate use during pregnancy and in women of childbearing age.

Background:

Modafinil and armodafinil (generic and branded products) are carve-out medications, paid for by fee-for-service (FFS), and designated as preferred agents on the Oregon Health Plan (OHA) preferred drug list (PDL). These agents are indicated for the treatment of excessive daytime sleepiness in both narcolepsy and obstructive sleep apnea (OSA) conditions. [1,2] Documented off-label uses of modafinil and armodafinil include fatigue associated with cancer, multiple sclerosis (MS) and other neurological conditions, depression, and other mood disorders.[3] Modafinil and armodafinil are regulated as class IV-controlled substances in the United States (US).[1,2] Both agents require a prior authorization (PA) to ensure medically appropriate use in adults for treatment of OHP-funded conditions. Previous reviews failed to identify any clinically significant comparative differences in efficacy or harms between modafinil, armodafinil, or other narcolepsy treatment agents.[4] However, in patients with OSA who were adherent to continuous positive airway pressure (CPAP), one systematic review with meta-analysis reported that modafinil or armodafinil therapy plus CPAP resulted in an increased proportion of patient dropouts due to adverse events compared to CPAP alone (6.2% vs. 2.8% respectively; RR 2.03; 95% CI 1.12 to 3.67; moderate quality evidence).[4,5] The most commonly reported adverse events were headache, vertigo and anxiety.[4,5]

Current FDA labeling designate both Provigil™ (modafinil) and Nuvigil™ (armodafinil) as Pregnancy Category C and advise that patients notify their physician if they become pregnant or intend to become pregnant.[1,2] These warnings were based on developmental toxicity observed at clinically relevant exposures in animal studies.[1,2] In 2009, the manufacturer of modafinil and armodafinil created a pregnancy registry currently linked on the FDA website to assist in data collection of adverse effects reported in pregnancy and fetal development.[6] In 2019, the EMA announced that they suspected congenital malformations were associated with modafinil use in pregnancy and recommended that the product should not be used in women who are pregnant, are planning to be pregnant, or are breastfeeding. [7] The alerts were identified by the manufacturer based on analysis of data from post-marketing pregnancy registry reports where congenital malformations were noted in up to 15% of children with modafinil exposure during pregnancy compared to 3% who were not exposed (see **Table 1**).[8] TEVA Canada Innovation released similar findings to Health Canada and cited a higher frequency of major congenital anomalies (17.3%) and cardiac anomalies (4%) in modafinil and/or armodafinil exposed patients compared to the general population (3% and 1%, respectively).[9] Health Canada has since updated their Canadian Product Monograph to include pregnancy as a contraindication to the use of modafinil.[9] Both Health Canada and the EMA also note that female patients of reproductive potential must instructed to use “effective contraception” during modafinil therapy but did not elaborate. The manufacturer has not issued such a warning to the FDA despite the data having been obtained through the US Nuvigil/Provigil Pregnancy Registry. At least one recent observational study has confirmed a similar association of exposure to modafinil and risk of major congenital malformations. [10]

Table 1. Recent Warnings for Modafinil and Armodafinil Use in Pregnancy

Year	Source	Warning	Recommendation
2019	Health Canada[9]	Risk of Congenital Anomalies - Based on international post-marketing reports, modafinil may cause fetal harm and is contraindicated in women who are pregnant or may become pregnant.	Healthcare professionals are advised to: • discuss with all female patients treated or to be treated with modafinil the potential risks associated with modafinil to a fetus during pregnancy • ensure all female patients of reproductive potential have a negative pregnancy test within a week before starting treatment with modafinil • instruct all female patients of reproductive potential that they must use effective contraception during therapy with modafinil, and for two months after discontinuation of modafinil treatment; • inform female patients that modafinil may reduce the effectiveness of steroidal [hormonal] contraceptives and that alternative or concomitant methods of contraception, other than steroidal [hormonal], are required during the modafinil treatment, and for two months after discontinuation of modafinil
2019	European Medicines Agency[7]	New product information wording - Based on limited human experience from a pregnancy registry and spontaneous reporting modafinil is suspected to cause congenital malformations when administered during pregnancy.	Updated warning in prescribing information: • modafinil is suspected to cause birth defects if taken during pregnancy. • Women of childbearing potential have to use effective contraception as modafinil may reduce the effectiveness of oral contraception, alternative additional methods of contraception are required. • If you are pregnant (or think that you may be), are planning to become pregnant, or are breast feeding, you should not take modafinil.

There have been post-marketing reports of serious adverse effects with armodafinil use.[11] Post-marketing reports have included 2 fatalities associated with drug hypersensitivity including drug reaction with eosinophilia and systemic symptoms.[11] Patients are advised to discontinue armodafinil at the first sign of rash, skin or mouth sores, blistering or ulceration.[11] In addition, hypersensitivity reactions such as Stevens-Johnson Syndrome have been documented with modafinil therapy.[12,13] Clinical trials and post market data noted increased rates of suicidal ideation associated with modafinil and armodafinil.[1,2] FDA labeling was updated to highlight the risk of psychiatric symptoms, including suicidal ideation, with armodafinil use.[1,2] Therefore, caution is advised when prescribing either of these agents in patients with a history of psychiatric symptoms such as documented psychosis, depression, and mania. [1,2] Prescribers are warned that these symptoms may result in hospitalization and to consider discontinuation of modafinil or armodafinil if psychiatric symptoms develop upon administration. [1,2]

Methods:

All adult patients (18 years or older) with a unique FFS claim for modafinil (HSN = 010865) or armodafinil (HSN = 034868) from January 2016 to May 2020 were included in the trend analysis (see **Figure 1**). Patients were only counted once total for analysis depending upon the first paid claim for either drug. Only patients with a new FFS claim for modafinil or armodafinil from 1/1/2018 to 12/31/2019 were included in the demographics, diagnostic, and safety analysis. The first FFS claim in the reporting period was classified as the index event (IE). Both FFS and CCO patients $\geq$ 18 years of age were included in the analysis if they had a FFS claim. Patients were excluded if they had Medicaid coverage for less than 75% of days in the 6 months before or after the first reference claim. Baseline characteristics, including patient age, were assessed at the time of the IE.

The following definitions and categories were used for the analysis of new start patients:

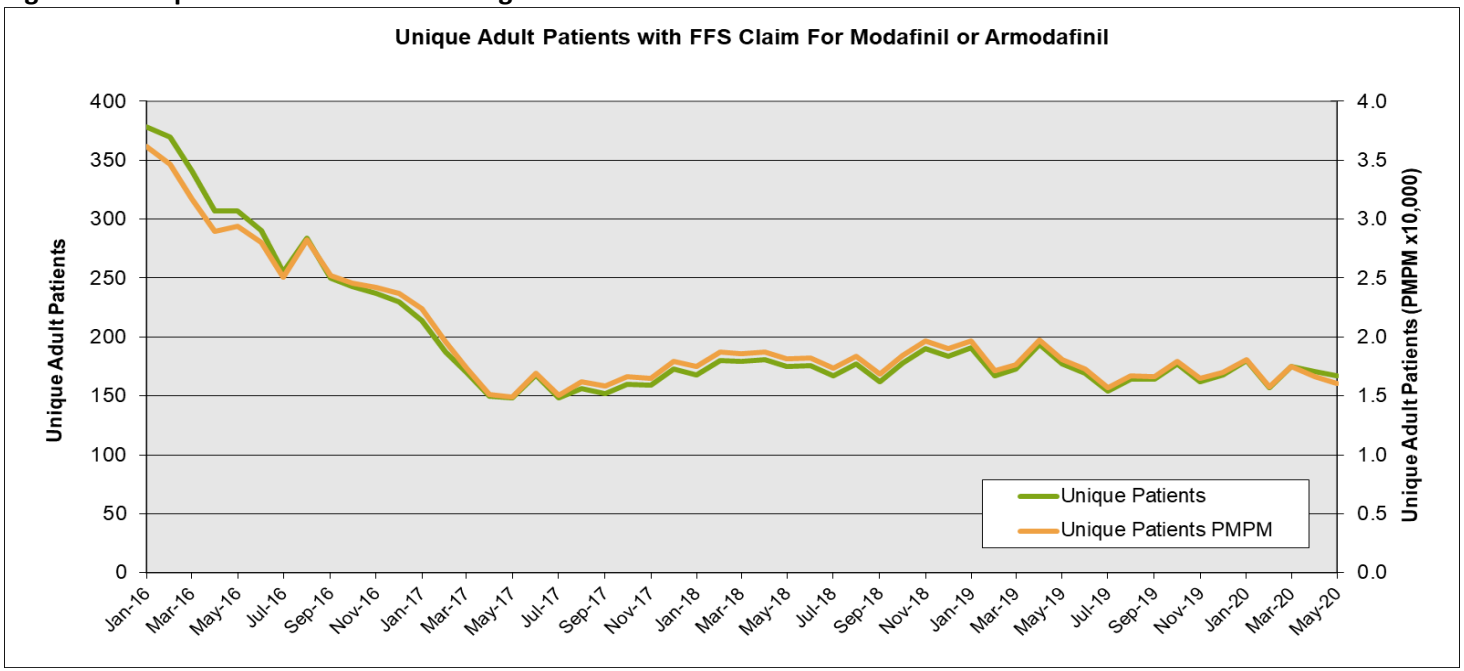
- New start patients were defined as patients without modafinil or armodafinil use in the 90 days prior to the IE.
- Prior history of modafinil/armodafinil use was evaluated in the 90 days prior to the IE.

- Comorbid diagnoses were identified using ICD-10 codes on medical claims in the 12 months before the IE (see **Appendix 1** for relevant ICD-10 codes).
- Drugs of Other Stimulant PDL class (modafinil, armodafinil) were identified based on HSN (010865 and 034868, respectively).
- Number of female patients of childbearing age (18-39) with no claims (Pharmacy or PAD) for a contraceptive agent in Standard Therapeutic Class 36 or 63 (e.g. diaphragms, condoms, nonoxynol 9/spemicide, or oral contaceptives [norgestrel, levonorgestrel, desogestrel, drospirenone, norethindrone, ethinyl estradiol, etc and combination products]) 4 months prior or 4 months after the first reference claim of reporting period in patients prescribed continuous modafinil/armodafinil therapy from January 1, 2018 to December 31, 2019.
- Continuous therapy patients were defined as those with sustained modafinil or armodafinil therapy for at least 90 days on either drug after index event in reporting period with no greater than 7 days between successive claim
- Patients with at least 1 medical claim for an adverse event within 30 days of therapy initiation.
- Patients with adverse events were identified 6 months prior to IE and up to 6 months after IE.
- New start patients with a pre-existing comorbidity who had an emergency room visit or hospitalization within 90 days following the IE.

Results:

Figure 1 indicates that after an initial decline in 2016, there have been roughly 150 to 200 unique patients with monthly FFS claims for modafinil or armodafinil for the past 3 years.

Figure 1 - Unique Patient Count with Drug Claim for Modafinil or Armodafinil



After exclusion of Medicare patients and patients without continuous Medicaid benefits (see **Appendix 2**), a total of 541 patients were identified as new start patients from 1/1/2018 to 12/31/2019. **Table 2** describes characteristics of patients prescribed modafinil or armodafinil with no prior history of use in the prior

90 days. Patients were primarily white females (65%) and approximately 44% were patients less than 40 years of age. Almost 75% of patients were prescribed modafinil compared to roughly 25% with armodafinil as their first index claim.

Table 2. Demographics for new start modafinil or armodafinil patients between 1/1/2018 to 12/31/2019.

		N= 541	%
Age (years)			
	Average (min - max)	41.5	(18-64)
	18-28	75	13.9%
	29-39	164	30.3%
	40-50	179	33.1%
	51 or older	123	22.7%
Female			
	Female	352	65.1%
	Male	189	34.9%
Race			
	White	321	59.3%
	Black	4	0.7%
	Native American	25	4.6%
	Other	8	1.5%
	Unknown	183	33.8%
Index Drug			
	Modafinil (HSN: 010865)	402	74.3%
	Armodafinil (HSN: 034868)	139	25.7%

Of the patients with new start prescriptions for modafinil or armodafinil, 157 patients were identified as females of childbearing age (18 to 39 years). Less than 2% (3/157) of females with childbearing potential had claims indicating a pregnancy diagnosis within 3 months of starting modafinil/armodafinil treatment.

Table 3 describes the number of female patients of childbearing age (18-39 years) who were identified as having continuous modafinil or armodafinil therapy. All included females were prescribed modafinil or armodafinil for at least 90 days after the first reference claim in the reporting period with no greater than 7 days between successive claims. Over three-quarters (77%) of these patients prescribed continuous modafinil/armodafinil therapy did not have evidence of birth control up to 4 months before and up to 4 months after starting therapy. Most of these women (60%) were 29-39 years of age, and 17% were 18-28 years of age.

Table 3. Continuous prescribing of Modafinil or Armodafinil therapy to women of childbearing age.

Female Patients Ages 18-39 on Continuous Therapy:	**N=**	**42**	**%**
Patients with sustained therapy and without birth control by age:			
18-28		7	17%
29-39		25	60%

Table 4a shows that the overall rate of patient ER visits within 3 months after starting modafinil/armodafinil was just over 18%, while the rate of hospitalizations was 2.4%. The rate of ER visits and hospitalizations prior to treatment were similar to post treatment rates. Based on clinical trial data, the FDA has identified several comorbidities associated with a high-risk of adverse outcomes when prescribed modafinil/armodafinil. **Table 4b** shows that over three-quarters of new-start patients (77%) had at least 1 claim to indicate the presence of a high-risk comorbidity present prior to therapy initiation. The most common high-risk comorbidity was mood disorder (62%), followed by anxiety disorder (42%), cardiovascular disease (29%), and psychosis (5%). In **Table 4c**, a subgroup analysis by comorbidity revealed that 27% of those with preexisting cardiovascular disease had an ER visit, whereas the rate in the 3 months before therapy was 17%. Interestingly, the rates of hospitalization for psychosis appeared to decrease with the initiation of modafinil/armodafinil therapy but the overall numbers were relatively small. All the other comparisons showed a 5% or less difference in the 90 day pre- and- post therapy initiation time period.

Table 4a. Patients with an ER visit or hospitalization up to 90 days after starting modafinil/armodafinil claim compared to 90 days prior to treatment.

		ER Visit		**Hospitalization**	
New start patients up to 90 days after therapy initiation	**N**	**N**	%	**N**	%
	541	99	(18.3%)	13	(2.4%)
New start patients in the 90 days prior to therapy initiation	541	91	(16.8%)	20	(3.6%)

Table 4b. Pre-existing high-risk comorbidities in new start modafinil/armodafinil patients.

	N **541**	**%**
Pre-existing comorbidity	416	77%
Cardiovascular disease	158	29%
Psychosis	25	5%
Other anxiety disorders	225	42%
Mood disorders	334	62%

Table 4c. Patients with preexisting comorbidity and ER visit or hospitalization rate 90 days before and after starting modafinil.

Pre-existing comorbidity	N	ER Visit Prior	ER Visit After	Hospitalization Before	Hospitalization After
Cardiovascular disease	158	27 (17%)	43 (27%)	9 (6%)	8 (5%)
Psychosis	25	7 (28%)	8 (32%)	5 (20%)	3 (12%)
Other anxiety disorders	225	48 (21%)	43 (19%)	13 (6%)	5 (2%)
Mood disorders	334	59 (18%)	58 (17%)	15 (4%)	8 (2%)

Table 5a lists adverse events identified within 30 days of modafinil/armodafinil therapy initiation. Of all patients with an adverse event within 30 days after therapy initiation, psychiatric symptoms were the most frequently reported (29% or 159/541) followed by 2% (10/541) with cardiovascular symptoms. No patients with hypersensitivity reactions or hepatic were identified. Upon subgroup analysis (**Table 5b**), most (143/159) of the psychiatric events were identified in patients 29 years or older with 40-50 year-olds having the highest proportion (56/159 or 35%) of all age subcategories. Only 10% of the cases were identified in patients 18 to 28 years of age. There were 4 deaths within the first month of therapy, 3 of whom were females and all of whom were 40 years or older. The causes of death were unknown.

Table 5a. New start patients with adverse event within 30 days of starting modafinil or armodafinil.

Adverse Event Type	Total Patients (N=541)	Male (N=189)	Female (N=352)
Psychiatric Symptoms	159 (29%)	52	107
Cardiovascular Symptoms	10 (2%)	4	6
Death	4 (<1%)	1	3

Table 5b. Adverse Events within 30 days of Modafinil/Armodafinil Therapy Initiation Separated by Age and Sex

Patients with >=1 Adverse Events by Age and Sex

	18-28 years		29-39 years		40-50 years		50+ years	
	N=75		N=164		N=179		N=123	
	M =28	F=47	M=54	F=110	M=58	F=121	M=49	F=74
Psychiatric Symptoms (N=159)	7	9	18	30	15	41	12	27
	16 (10%)		48 (30%)		56 (35%)		39 (25%)	
Cardiovascular Symptoms (N=10)	1	1	1	0	1	3	1	2
	2 (20%)		1 (10%)		4 (40%)		3 (30%)	
Death (N=4)	0	0	0	0	0	2	1	1
	0		0		2 (50%)		2 (50%)	

As stated previously, the FDA has identified numerous adverse events associated with modafinil/armodafinil use. **Table 6** identifies new adverse events reported up to 6 months after modafinil/armodafinil therapy initiation in patients without a prior history of the diagnosis. Medical claims for one or more of these adverse events occurred in about 12% of patients. Roughly 9% of individuals with a documented psychiatric adverse event after modafinil/armodafinil therapy initiation had no prior claims history of these symptoms in the 6 months prior to treatment initiation. New cardiovascular events were noted in 3-4% of patients. There were few to no claims for new hypersensitivity reactions or hepatic symptoms.

Table 6. Number of Patients with Adverse Events in the 6 months after Index Event, but no adverse event in 6 months prior.

	Modafinil		Armodafinil	
Adverse Event Type	**402**	**%**	**139**	**%**
Hypersensitivity reactions	1	0.2%		0.0%
Psychiatric Symptoms	34	8%	12	9%
Cardiovascular Symptoms	14	4%	4	3%
Total number of patients with Adverse Event	49	12.2%	16	12%

Limitations:

Data presented in this report is based on Medicaid claims history and has several inherent limitations.

- Definitions for new start patients: Prior use of modafinil/armodafinil was only evaluated in the 90 days prior to the IE. Patients could have had a remote history of modafinil/armodafinil use beyond this date which could influence choice in current therapy.
- Diagnostic accuracy: Diagnoses based on claims history may be inaccurate or incomplete. Many patients in this analysis may have been enrolled in coordinated care organizations and delays in submission and processing of medical claims data may result in missed diagnoses. Diagnosis codes for pregnancy may not have been fully captured as miscarriages and/or elective termination of pregnancy were not analyzed. Assumptions regarding child-bearing potential may have led to incomplete data as women 40 years of age or older of gestational viability were excluded from analysis. In addition, contraceptive mechanisms through other payment sources (eg. third-party payors), health status (eg. prior hysterectomy or sterile), male partner status (eg. vasectomy), life-choices (eg. not sexually active), or other contraceptive products either not obtained at pharmacy point of sale or non-prescription (eg. intrauterine device, barrier) were not captured in the claims data. These alternative forms of contraception may be more common in this population as there is a drug interaction with modafinil/armodafinil and hormonal contraception.
- Adverse events: This study did not analyze all reported adverse events, or every high-risk comorbidity identified by FDA or post-marketing data. Psychiatric adverse events included the broad categories of psychosis, anxiety, and mood disorders which made it difficult to detect the frequency of specific reactions possibly associated with modafinil/armodafinil use.
- Correlation of adverse events: There is no way to determine if the adverse events identified via claims were definitively associated with modafinil/armodafinil use.
- Small sample size: more patients may be needed to observe correlations between modafinil/armodafinil exposure and adverse outcomes.

References:

1. Provigil prescribing information. Cephalon Inc., Frazier, PA. January 2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf. Accessed June 29, 2020.
2. Nuvigil prescribing information. Cephalon Inc., Frazier, PA. April 2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021875s021lbledt.pdf. Accessed June 29, 2020.
3. Micromedex Healthcare Series [internet database]. Greenwood Village, CO: Truven Health Analytics, Inc. Updated periodically. Accessed July 30, 2020
4. Drug Class Update with New Drug Evaluation: Narcolepsy Agents, Author: Servid S, February 2020.
5. Avellar ABCC, Carvalho LBC, et al. Pharmacotherapy for residual excessive sleepiness and cognition in CPAP-treated patients with obstructive sleep apnea syndrome: A systematic review and meta-analysis. Sleep Med Rev. 2016;30:97-107.
6. Food and Drug Administration. List of Pregnancy Exposure Registries. Updated June 12, 2020. https://www.fda.gov/science-research/womens-health-research/list-pregnancy-exposure-registries. Accessed June 18, 2020.
7. European Medicines Agency. PRAC recommendations on signals. May 6, 2019. https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-8-11-april-2019-prac-meeting_en.pdf. Accessed June 18, 2020.
8. Teva Pharmaceuticals Ireland. Direct Healthcare Professional Communication (DHPC). Modafinil: potential risk of congenital malformations when administered during pregnancy. June 7, 2019. http://www.hpra.ie/docs/default-source/default-document-library/important-safety-information---modafinil99170c2697826eee9b55ff00008c97d0.pdf?. Accessed June 18, 2020.
9. Government of Canada, Health Canada. ALERTEC (modafinil) and the Risk of Congenital Anomalies. June 20, 2019. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2019/70201a-eng.php. Accessed June 18, 2020.
10. Damkier P, Broe A. First-Trimester Pregnancy Exposure to Modafinil and Risk of Congenital Malformations. JAMA. 2020;323(4):374–376.
11. Nuvigil (Armodafinil) FDA Safety-related labeling changes Approved by FDA Center for Drug Evaluation and Research (CDER) Feb 07 2017 (SUPPL-23). https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=828. Accessed June 18, 2020.
12. Holfinger S, Roy A, Schmidt M. Stevens-Johnson syndrome after armodafinil use. J Clin Sleep Med. 2018;14(5):885–887.
13. Prince V, Philippidou M, et al. Stevens-Johnson syndrome induced by modafinil. Clin Exp Dermatol. 2018;43(2):191-192.

Appendix 1: Definitions

ICD-10 Definitions

Diagnoses indicating pregnancy	O00-O9Ax, Z331, Z34x
Comorbidities	
Cardiovascular	
Hypertension diagnosis	I10, I15x
Myocardial infarction	I21x
Unstable angina	I20x
Psychosis	F20x-F29x
Other Anxiety disorders	F41x
Mood disorder	F30x-F39x
Adverse Events	
Hypersensitivity Reactions	
Drug rash	L27x
Stevens-Johnson Syndrome	L511
Toxic Epidermal Necrolysis	L512
Stevens-Johnson-toxic epidermal necrolysis overlap syndrome	L513
Angioedema	T783x
Anaphylaxis	T782x
Unspecified adverse effect of drug	T887x
Multi-organ hypersensitivity	R652
Psychiatric Symptoms	
Stimulant dependence w/ stimulant-induced psychotic disorder w/ hallucinations	F15251
Psychosis	F20x-F29x
Anxiety	F41x
Mood disorders	F30x-F39x
Hallucinations and symptoms w/ general sensations and perceptions	R44x
Suicidal ideation or suicide attempt	R4585x, T1491x
Cardiovascular Symptoms	
Angina	I20x
Palpitations	R002
Dyspnea	R060x
Transient ischemia	G459
Hepatic Symptoms	
Hepatitis	K72x
Toxic liver disease	K71x

Appendix 2: Exclusions

DUE Benefit Package Exclusion List
BMM – QMB + OHP with Limited Drug Package
BMD – OHP with Limited Drug
CWM – Emergency services only – Citizen Alien Waived Emergent Medical (CAWEM)
MED – Qualified Medicare Beneficiary (Dual)
MND – Transplant Package
SMF – Special Low Income Medicare Beneficiary Only (no Medicaid drug benefit)
SMB – Special Low Income Medicare Beneficiary Only (no Medicaid drug benefit)

Appendix 3: Proposed Prior Authorization Criteria Updates

Sleep-Wake Medications

Goal(s):
- To promote safe use of drugs for obstructive sleep apnea and narcolepsy.
- Limit use to diagnoses where there is sufficient evidence of benefit and uses that are funded by OHP. Excessive daytime sleepiness related to shift-work is not funded by OHP.
- Limit use to safe doses.

Length of Authorization:
- Initial approval of 90 days if criteria met; approval of up to 12 months with documented benefit

Requires PA:
Payment for drug claims for modafinil or armodafinil without previous claims evidence of narcolepsy or obstructive sleep apnea
Solriamfetol
Pitolisant

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Funded Indications.

Indication	Modafinil (Provigil™)	Armodafinil (Nuvigil™)	Solriamfetol (Sunosi™)	Pitolisant (Wakix™)
• Excessive daytime sleepiness in narcolepsy	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older
• Residual excessive daytime sleepiness in obstructive sleep apnea patients treated with CPAP.	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	Not FDA approved; insufficient evidence
• Depression augmentation (unipolar or bipolar I or II acute or maintenance phase) • Cancer-related fatigue • Multiple sclerosis-related fatigue	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence
• Drug-related fatigue • Excessive daytime sleepiness or fatigue related to other neurological disorders (e.g. Parkinson's Disease, traumatic brain injury, post-polio syndrome) • ADHD • Cognition enhancement for any condition	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence

Table 2. Maximum Recommended Dose (consistent evidence of benefit with lower doses).

Generic Name	Minimum Age	Maximum FDA-Approved Daily Dose
Armodafinil	18 years	250 mg
Modafinil	18 years	200 mg
Solriamfetol	18 years	150 mg
Pitolisant	18 years	17.8 mg (poor CYP2D6 metabolizers)

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Is the patient 18 years of age or older?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness. Providers for patients 7 to 17 years of age may also submit a request for sodium oxybate as it is FDA-approved for narcolepsy in this age group.
3. Is this a funded diagnosis? Non-funded diagnoses: • Shift work disorder (ICD10 G4720-4729; G4750-4769; G478) • Unspecified hypersomnia (ICD10 G4710)	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by OHP
4. Is the request for continuation of therapy at maintenance dosage previously approved by the FFS program?	**Yes:** Go to Renewal Criteria	**No:** Go to #5
5. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., sleep specialist, neurologist, or pulmonologist)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Will prescriber consider a preferred alternative?	**Yes:** Inform prescriber of preferred alternatives (e.g., preferred methylphenidate)	**No:** Go to #7
7. Is the prescribed daily dose higher than recommended in Table 2?	**Yes:** Go to #8	**No:** Go to #9

Approval Criteria		
8. Is the request for pitolisant in a patient with documentation of all the following: • CYP2D6 testing which indicates the patient is not a poor metabolizer • Chart notes or provider attestation indicating lack of hepatic or renal impairment	**Yes:** Go to #9 Max dose for pitolisant is 35.6 mg daily.	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is there baseline documentation of fatigue severity using a validated measure (e.g., Epworth score, Brief Fatigue Inventory, or other validated measure)?	**Yes:** Go to #10 Document baseline scale and score	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the request for solriamfetol or pitolisant?	**Yes:** Go to #11	**No:** Go to #15
11. Does the patient have a diagnosis of end stage renal disease?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #12
12. Is the request for solriamfetol?	**Yes:** Go to #13	**No:** Go to #15
13. Is the request for concurrent use with a monoamine oxidase inhibitor?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14
14. Is there documentation of a recent cardiovascular risk assessment (including blood pressure) with physician attestation that benefits of therapy outweigh risks?	**Yes:** Go to #17 Document recent blood pressure within the last 3 months and physician attestation of cardiovascular risk assessment	**No:** Pass to RPh. Deny; medical appropriateness Use of solriamfetol is not recommended in patients with uncontrolled hypertension or serious heart problems.
15. Is the patient a woman with childbearing potential?	**Yes:** Go to #16	**No:** Go to #17
16. If appropriate, is there documentation of a negative pregnancy test as well as reliable contraception OR documentation that provider has assessed pregnancy risk and discussed contraceptive use with the patient?	**Yes:** Go to #17	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
17. Is the request for treatment of narcolepsy for a drug FDA-approved for the condition (Table 1)?	**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	**No:** Go to #18
18. Is the request for treatment of obstructive sleep apnea (OSA) (without narcolepsy) for a drug FDA-approved for the condition (see Table 1)?	**Yes:** Go to #19	**No:** Go to #20
19. Is the patient compliant with recommended first-line treatments (e.g., CPAP or other primary therapy)?	**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	**No:** Pass to RPh; Deny; medical appropriateness
20. Is the request for off-label use of armodafinil, solriamfetol, or pitolisant (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness. There is insufficient evidence for off-label use.	**No:** Go to #21
21. Is the primary diagnostic indication for modafinil fatigue secondary to major depression (MDD), MS or cancer-related fatigue? Note: Methylphenidate is recommended first-line for cancer.	**Yes:** Inform prescriber of first-line options available without PA. May approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit and assessment of adverse effects.	**No:** Go to #22

Approval Criteria
22. All other diagnoses must be evaluated as to the OHP-funding level and evidence for clinical benefit. • Evidence supporting treatment for excessive daytime sleepiness (EDS) or fatigue as a result of other conditions is currently insufficient and should be denied for “medical appropriateness”. • Evidence to support cognition enhancement is insufficient and should be denied for “medical appropriateness”. If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.

Renewal Criteria		
1. Is the request for solriamfetol?	**Yes:** Go to #2	**No:** Go to #3
2. Is there documentation of a recent blood pressure evaluation (within the last 3 months)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for treatment of obstructive sleep apnea?	**Yes:** Go to #4	**No:** Go to #5
4. Is the patient adherent to primary OSA treatment (e.g.,CPAP) based on chart notes?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is there documentation of clinical benefit and tolerability from baseline? The same clinical measure used to diagnose excessive daytime sleepiness (EDS), fatigue secondary to MS and/or cancer, major depressive disorder (MDD) is recommended to document clinical benefit. For Epworth Sleepiness Scale, and improvement of at least 3 points is considered clinically significant.	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *10/1/2020(DE); 2/2020; 7/19; 03/16; 09/15*
Implementation: *11/1/20; 3/1/2020; 8/19/19; 8/16, 1/1/16*