August 21, 2023

Re: October 5, 2023 Medicaid P&T Committee; Ensuring Equitable Access to Leqembi®

Dear Committee Members:

I am writing today on behalf of the Alzheimer's Association to ask that the Oregon Pharmacy and Therapeutics (P&T) Committee make a coverage decision that allows equitable access to Medicaid coverage for Leqembi® at the next meeting. The Alzheimer's Association asks the Committee to recommend access to Leqembi that follows the *Lecanemab: Appropriate Use Recommendations*[1] developed by the Alzheimer's Disease and Related Disorders Therapeutics Work Group. Each day without access to the drug, the Alzheimer's Association estimates more than 2,000 individuals aged 65 or older transition from mild dementia due to Alzheimer's to a more advanced stage of the disease where they will no longer be eligible for Leqembi. Therefore, missing the opportunity to see improved outcomes or clinical benefits at the early stages of their disease progression.

As you are aware, lecanemab (Leqembi) received traditional approval from the FDA on July 6th, 2023 as a treatment for early stage Alzheimer's disease. Leqembi is the second in a new category of medications approved for the treatment of Alzheimer's disease that target the fundamental pathophysiology of the disease. This medication represents an important advancement in the ongoing fight to effectively treat Alzheimer's disease. On behalf of those living with Alzheimer's disease and their families, the Alzheimer's Association continues to call on regulating bodies to provide access to monoclonal antibodies targeting amyloid for the treatment of Alzheimer's disease, including Leqembi.

The Alzheimer's Association leads the way to end Alzheimer's and all other dementia — by accelerating global research, driving risk reduction and early detection, and maximizing quality care and support. As the leading voluntary health organization in Alzheimer's care, support and research, the Alzheimer's Association is dedicated to promoting care considerations that lead to improved patient outcomes and committed to ensuring that evidence-based practices for the diagnosis and care of Alzheimer's disease are available to all individuals living with Alzheimer's.

Currently more than 69,000 individuals in Oregon are living with Alzheimer's disease, and over 168,000 family members and friends are providing care to their loved ones. On behalf of those living with Alzheimer's disease and their families, the Alzheimer's Association asks that the Oregon Pharmacy and Therapeutics (P&T) Committee allow equitable access to Leqembi. As an FDA-approved treatment for people with early-stage Alzheimer's, access to coverage should be available to Oregon Medicaid beneficiaries living with this disease. Ensuring access to this new treatment may mean prolonging the earliest stages of this disease, prior to significant cognitive and functional decline.

Sincerely,

Chris Madden
Director of Public Policy
Alzheimer's Association - Oregon Chapter

[1] Cummings, J., Apostolova, L., Rabinovici, G.D. et al. Lecanemab: Appropriate Use Recommendations. *J Prev Alzheimers Dis* (2023). https://doi.org/10.14283/jpad.2023.30

OPVEE® (nalmefene) nasal spray

To Whom it May Concern:

Thank you for your interest in OPVEE® (nalmefene) nasal spray. As requested, an overview of OPVEE®, including the clinical development program and safety, is provided below. Please see the full Prescribing Information for complete efficacy and safety data. Should you wish to discuss further, please contact your Indivior Medical Outcomes and Value Liaison (MOVL).

OPVEE® is for emergency treatment of known or suspected overdose induced by natural or synthetic opioids in patients 12 years and older, as manifested by respiratory and/or central nervous system depression. OPVEE® is for immediate administration as emergency therapy in settings where opioids may be present and is not a substitute for emergency medical care.

OPVEE® is contraindicated in patients who are allergic to nalmefene or any of the other ingredients. Additional Important Safety Information is provided later in the document.

OPVEE® is for intranasal use only, in a ready to use device with no assembly required. OPVEE® does not need to be primed prior to administration. OPVEE® delivers its entire contents automatically, upon activation. OPVEE® should not be reused as each unit-dose device contains a single dose of nalmefene.

OPVEE® should be administered as quickly as possible because prolonged respiratory depression may result in damage to the central nervous system or death and emergency medical assistance should be sought after administration of the first dose of OPVEE® in the event of a suspected, potentially life-threatening opioid emergency. Patients should remain under continued surveillance until emergency personnel arrive. Additional doses of OPVEE® may be required until emergency medical assistance becomes available. OPVEE® may be re-administered using a new nasal spray, in the nose, every 2 to 5 minutes if the patient does not respond or responds and then relapses into respiratory depression. OPVEE® should be administered according to the printed instructions on the Quick Start Guide and the Instructions for Use.

OPVEE® is available as a unit-dose nasal spray that delivers available as 2.7 mg nalmefene (equivalent to 3 mg of nalmefene hydrochloride) in 0.1 mL. Each carton contains two unit-dose nasal spray devices.

Please continue to next page for more information on the clinical development program and safety.

PHARMACOKINETIC (PK) STUDIES (OPNT003-PK-001 and OPNT003-PK-002)

PHARMACOKINETIC EVALUATION OF INTRANASAL NALMEFENE (OPNT003-PK-001)

Study Overview

- In a cross-over pharmacokinetic study of 68 healthy adult volunteers, the relative bioavailability of one 2.7 mg OPVEE® nasal spray in one nostril was compared to a single dose of nalmefene 1.0 mg administered as an intramuscular injection. The pharmacokinetic parameters obtained in this study are shown in Table 1 and the plasma concentration time profiles are presented in Figure 1. The safety and tolerability of OPVEE® was also evaluated.

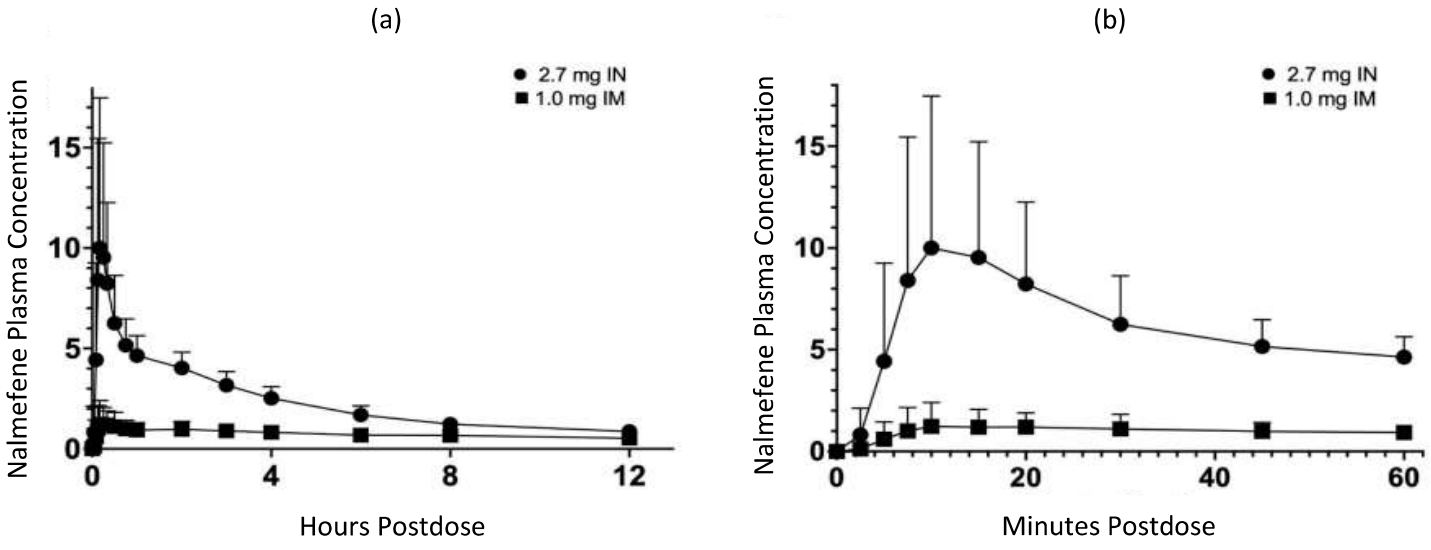
Study Results

Table 1: PK Parameters of Nalmefene after IN Administration of 2.7 mg OPVEE® and IM Administration of 1.0 mg of Nalmefene

PK parameters	OPVEE® 2.7 mg	Nalmefene IM 1.0 mg
T_{max} (h)[a]	0.250 (0.0833-2.00)	0.33 (0.117-18.0)
C_{max} (ng/mL)[b]	10.4 (62.6)	1.50 (59.4)
$T_{1/2}$ (h)[b]	11.4 (20.8)	10.6 (18.5)
F_{rel}[b]	0.806 (10.9)	NA

[a]: T_{max} (h): Time to reach max concentration in hours—presented as median (range); [b]: Arithmetic mean (Coefficient of variation percentage); C_{max}(ng/mL): Max concentration; F_{rel} : Mean bioavailability; IM: Intramuscular; IN: Intranasal; NA: Not applicable; $T_{1/2}$ (h): Half-life in hours.

Figure 1: Mean Plasma Concentration-Time Profiles of Nalmefene (a) 0-12 hours and (b) 0-60 minutes Following IN Administration of OPVEE® (2.7 mg) and IM Injection of Nalmefene (1.0 mg)



Values represent the mean and standard deviation (n=68)

- Most common adverse reactions were nasal discomfort and dizziness.
- The relative frequencies of treatment-related common adverse events that occurred in greater than 5% of healthy adult volunteers in OPNT003-PK-001 are presented in Table 3 on page 5.

PHARMACOKINETIC EVALUATION OF INTRANASAL NALMEFENE USING THREE DOSING REGIMENS (OPNT003-PK-002)

Study Overview

- In a second cross-over pharmacokinetic study of 24 healthy adult volunteers, the pharmacokinetics of OPVEE® were evaluated when given as three different dosing regimens. The safety and tolerability of OPVEE® was also evaluated.
- Volunteers were exposed to one spray of OPVEE® in one nostril, one spray of OPVEE® in each nostril, and two sprays of OPVEE® in one nostril.

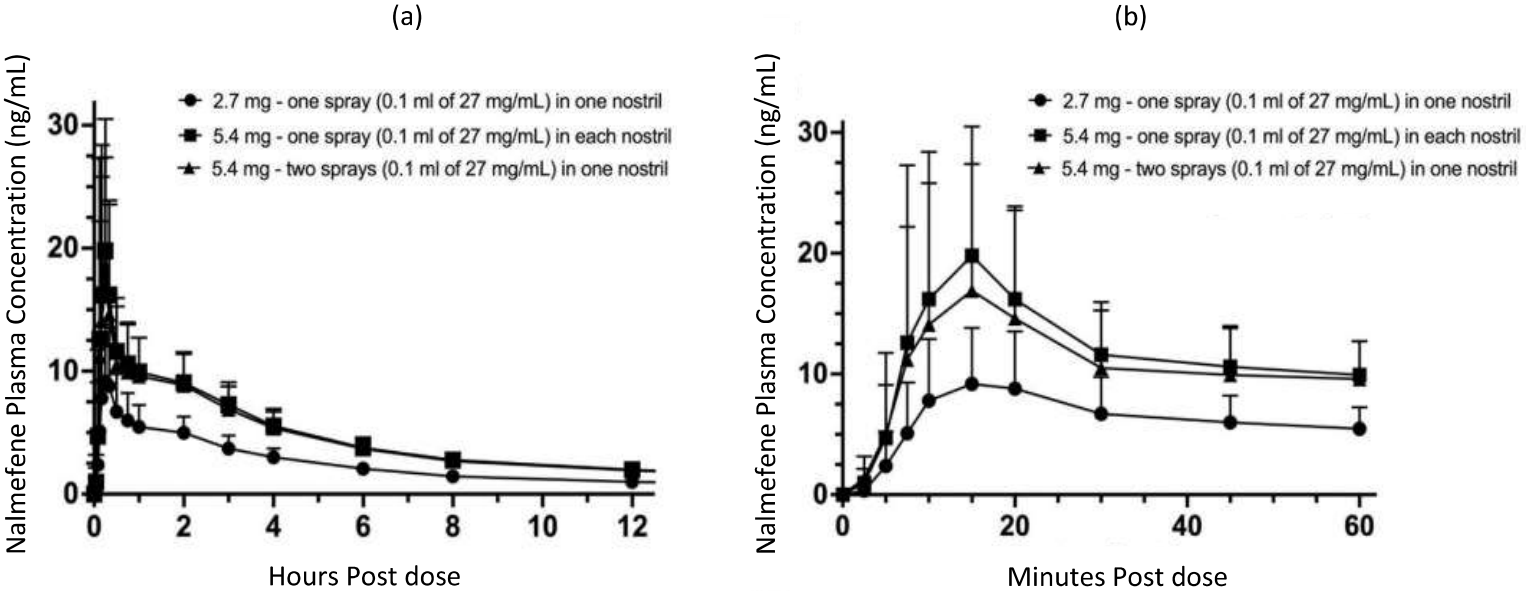
Study Results

Table 2: PK Parameters of Nalmefene After IN Dose of 2.7 mg Nalmefene (One OPVEE® nasal spray in One Nostril), IN Dose of 5.4 mg Nalmefene (One OPVEE® nasal spray in Each Nostril) and IN Dose of 5.4 mg Nalmefene (Two OPVEE® nasal sprays in One Nostril)

PK parameters	OPVEE® 2.7 mg (one spray)	IN Nalmefene 5.4 mg (one OPVEE® spray in each nostril)	IN Nalmefene 5.4 mg (two OPVEE® sprays in one nostril)
T_{max} (h)[a]	0.267 (0.167-2.03)	0.250 (0.117-3.00)	0.250 (0.117-2.03)
C_{max} (ng/mL)[b]	9.75 (49.4)	18.9 (88.0)	16.1 (62.9)
$T_{1/2}$ (h)[c]	11.4 (22.0)	11.3 (16.6)	11.3 (16.5)

[a]: T_{max} (h): Time to reach max concentration in hours—presented as median (range); [b]: C_{max}(ng/mL): Max concentration—presented as geometric mean (coefficient of variation percentage); [c]: $T_{1/2}$ (h): Half-life in hours—presented as arithmetic mean (coefficient of variation percentage); IN: Intranasal.

Figure 2: Mean Plasma Concentration of Nalmefene, (a) 0-12 hours and (b) 0-60 minutes Following IN Administration of 2.7 mg Nalmefene (One OPVEE® nasal spray in One Nostril), IN Dose of 5.4 mg Nalmefene (One OPVEE® nasal spray in Each Nostril) and IN Dose of 5.4 mg Nalmefene (Two OPVEE® nasal sprays in One Nostril)



Values represent the mean and standard deviation (n=24)

- Most common adverse reactions were pain in the nose, nasal congestion, nasal discomfort and nausea.
- The relative frequencies of treatment-related common adverse events that occurred in greater than 5% of healthy adult volunteers in OPNT003-PK-002 are presented in Table 3 on page 5.

PHARMACODYNAMIC (PD) STUDY (OPNT003-OOD-001)

PHARMACODYNAMIC EVALUATION OF INTRANASAL NALMEFENE (OPNT003-OOD-001)

Study Overview

- The effect of 2.7 mg OPVEE® on remifentanil-induced respiratory depression in an experimental ventilatory-response to hypercapnia model, assessed by changes in minute ventilation (MV), was evaluated in 61 opioid-experienced, non-dependent volunteers.
- Volunteers received a hypercapnic gas mixture (50% O2, 43% N2, 7% CO2) at -25 minutes. Just prior to initiation of remifentanil infusion at -15 minutes is the baseline MV (marked as 100% in Figure 3 and marked as observed data as liters/minute in Figure 4).
- Fifteen minutes after initiating remifentanil infusion, nadir in MV is observed at time zero, at which point OPVEE® was administered. The subjects were then monitored for changes in MV over 120 minutes.

Study Results

- Following OPVEE® administration the time to onset of effect, that is onset of reversal of respiratory depression, was observed between 2.5 to 5 minutes (Figure 3 and Figure 4).
- At 5 minutes the estimated mean increase in MV was 5.745 L/min (Figure 3).
- Full recovery of respiratory drive was noted between 5 and 15 minutes after OPVEE® administration (Figure 3 and Figure 4).

Figure 3: Percentage recovery of respiratory drive after infusion of remifentanil in CO2 stimulated MV (mean +/- SD) in adult healthy volunteers treated with OPVEE®

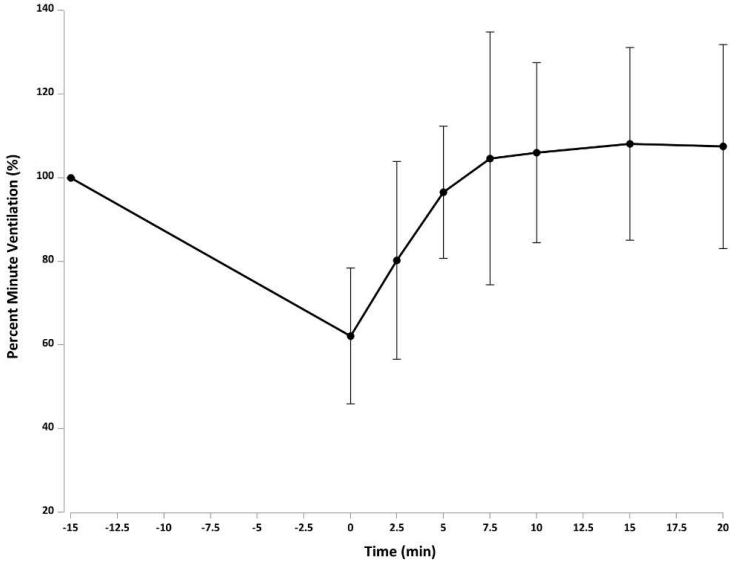
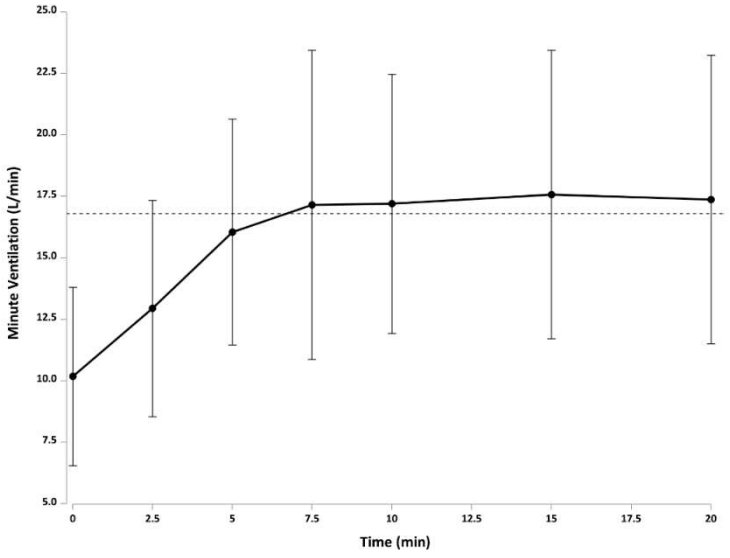


Figure 4: Reversal of Remifentanil-Induced Respiratory Depression (Mean MV +/- SD) by OPVEE®



Remifentanil (an initial bolus of 0.5 µg/kg dose followed by an infusion rate of 0.175 µg/kg/min) was administered for 15 min prior to test agents and continued for the duration of the study. In Figure 4, the dashed line represents the mean minute ventilation (MV) prior to remifentanil administration.
CO2: carbon dioxide; Min: minute; MV: minute ventilation; SD: standard deviation

- Most common adverse reactions were headache, nausea, hot flush and dizziness.
- The relative frequencies of treatment-related common adverse events that occurred in greater than 5% of healthy adult volunteers in OPNT003-OOD-001 are presented in Table 3 on page 5.

SAFETY OUTCOMES FOR PK AND PD STUDIES (OPNT003-PK-001, OPNT003-PK-002, AND OPNT003-OOD-001)

Table 3: Relative Frequencies of Treatment-Related Common Adverse Events That Occurred in Greater Than 5% of Healthy Adult Volunteers

System Organ Class Preferred Term	OPVEE® 2.7 mg			IN Nalmefene 5.4 mg	
	Total 2.7 mg n (%)	PD Study n (%)	PK Studies n (%)	PK Study (One OPVEE® spray in each nostril) n (%)	PK Study (Two OPVEE® sprays in one nostril) n (%)
Total	**N=150**	**N=61**	**N=89**	**N=23**	**N=24**
Respiratory, thoracic and mediastinal disorders					
Nasal discomfort	43 (28.7%)	5 (8.2%)	38 (42.7%)	3 (13.0%)	3 (12.5%)
Nasal congestion	6 (4.0%)	2 (3.3%)	4 (4.5%)	1 (4.3%)	4 (16.7%)
Rhinalgia (pain in the nose)	4 (2.7%)	1 (1.6%)	3 (3.4%)	2 (8.7%)	6 (25.0%)
Nervous system disorders					
Headache	40 (26.7%)	34 (55.7%)	6 (6.7%)	1 (4.3%)	0
Dizziness	14 (9.3%)	9 (14.8%)	5 (5.6%)	0	1 (4.2%)
Gastrointestinal disorders					
Nausea	25 (16.7%)	22 (36.1%)	3 (3.4%)	5 (21.7%)	1 (4.2%)
Vomiting	9 (6.0%)	7 (11.5%)	2 (2.2%)	1 (4.3%)	0
Vascular disorders					
Hot flush	12 (8.0%)	12 (19.7%)	0	0	0
Psychiatric disorder					
Anxiety	7 (4.7%)	7 (11.5%)	0	0	0
Skin and subcutaneous tissue disorders					
Hyperhidrosis (increased sweating)	3 (2.0%)	3 (6.6%)	0	0	1 (4.2%)

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS

Risk of Recurrent Respiratory and Central Nervous System Depression: While the duration of action of nalmefene is as long as most opioids, a recurrence of slowed breathing (respiratory depression) is possible after treatment with OPVEE®. Watch patients and give repeat doses of OPVEE® using a new device, as necessary, while awaiting emergency medical assistance.

Risk of Limited Efficacy with Partial Agonists or Mixed Agonists/Antagonists: Improvement in respiratory depression caused by medicines such as buprenorphine and pentazocine may not be complete. Repeat doses of OPVEE® may be required.

Precipitation of Severe Opioid Withdrawal: Use in patients who are opioid dependent may cause symptoms of opioid withdrawal like body aches, fever, sweating, runny nose, sneezing, goose bumps, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, and rapid heart rate. Some patients may become aggressive when an opioid overdose is treated.

Abrupt postoperative reversal of opioid depression may result in adverse cardiovascular (CV) effects. These events have primarily occurred in patients with preexisting CV disorders or who received other drugs with similar adverse CV effects. Monitor these patients closely in an appropriate healthcare setting.

In newborns, opioid withdrawal may be life-threatening if not recognized and properly treated and may also include convulsions, excessive crying, and hyperactive reflexes.

Risk of Opioid Overdose from Attempts to Overcome the Blockade: Taking large or repeated doses of opioids, such as heroin or prescription pain pills to overcome blockade, may lead to opioid intoxication and death.

ADVERSE REACTIONS

Most common adverse reactions (incidence at least 2%) are nasal discomfort, headache, nausea, dizziness, hot flush, vomiting, anxiety, fatigue, nasal congestion, throat irritation, pain in the nose, decreased appetite, changes in sense of taste, skin redness, and increased sweating.

To report a pregnancy or side effects associated with taking OPVEE® or any safety related information, product complaint, request for medical information, or product query, please contact PatientSafetyNA@indivior.com or 1-877-782-6966.

See accompanying full Prescribing Information, or for more information about OPVEE®, visit www.OPVEE.com.

References:

1. Prescribing Information for OPVEE®.