CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217389Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	217389
PDUFA Goal Date	June 26, 2024
Nexus TTT #	2023-5268
Reviewer Name	Leah Hart, PharmD
Team Leader	Carolyn Tieu, PharmD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	June 12, 2024
Subject	Evaluation of Need for a REMS
Established Name	Ensifentrine
Trade Name	Ohtuvayre
Name of Applicant	Verona Pharma, Inc.
Therapeutic Class	Phosphodiesterase 3 (PDE3) inhibitor and phosphodiesterase 4 (PDE4) inhibitor
Formulation(s)	Inhalation Suspension
Dosing Regimen	3 mg two daily by oral inhalation via nebulizer

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Ohtuvayre (ensifentrine) is necessary to ensure the benefits outweigh its risks. Verona Pharma, Inc. submitted a New Drug Application (NDA) 217389for Ohtuvayre with the proposed indication for the maintenance treatment of chronic obstructive pulmonary disease (COPD). The draft labeling states that Ohtuvayre is not for use for the relief of acute bronchospasm, as it has not been studied in the relief of acute symptoms, other risks associated with Ohtuvayre include paradoxical bronchospasm and psychiatric events including suicidality. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM has determined that a REMS is not needed to ensure the benefits of Ohtuvayre outweigh its risks. The review team concluded that the improvement in the pulmonary function with Ohtuvayre showed benefit for the treatment of COPD in adult patients. The risks associated with the use of Ohtuvayre are included in other products approved for the treatment of COPD. The likely prescribers will most likely have the knowledge and experience to diagnose, monitor, and manage these risks. These risks will be communicated in the Warnings and Precautions section of the Prescribing Information with instructions to providers what to do if the patient experiences any of the risks associated with Ohtuvayre.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Ohtuvayre (ensifentrine) is necessary to ensure the benefits outweigh its risks. Verona Pharma, Inc. submitted a New Drug Application (NDA) 217389 for Ohtuvayre with the proposed indication for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adult patients. This application is under review in the Division of Pulmonary, Allergy, and Critical Care. The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Ohtuvayre (ensifentrine), a new molecular entity, is a phosphodiesterase 3 (PDE3) and phosphodiesterase 4 (PDE4) inhibitor proposed for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adult patients. [a,b] Ohtuvayre is proposed as an oral inhalation suspension

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

intended for both inpatient and outpatient use. Ohtuvayre is not currently approved in any jurisdiction and is the first in class.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 217389 relevant to this review:

- 06/26/2023: NDA 217389 submission for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adult patients received
- 11/29/2023: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for Ohtuvayre

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Chronic obstructive pulmonary disease (COPD) is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as a heterogenous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration, and/or exacerbations) due to abnormalities of the airway (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction.[1] Risk factors for COPD include environmental, genetics, lung function trajectories: lung development and aging, socioeconomic status, and history of infections.[1]Forced vital capacity maneuver during spirometry showing the presence of a post bronchodilator FEV_1/FVC ration <0.7 is needed to establish the diagnosis of COPD.[1] The severity of airflow obstruction is classified as GOLD grades 1 (mild), 2 (moderate), 3 (severe), and 4 (very severe) and the symptom and risk components are combined to categorize patients into one of three groups[1]:

- Group A: Less symptomatic, low risk of future exacerbations (zero to one exacerbation without hospitalization)
- Group B: More symptomatic, low risk of future exacerbations (zero to one exacerbation without hospitalization)
- Group E: High risk of future exacerbations (≥2 exacerbations per year or ≥1 hospitalization for exacerbation)

The American Lung Association estimates that in 2021, 138,825 people died from COPD, making it the sixth overall leading cause of death with 85% of those deaths occurring in those age 65 years or older. [c,2] The CDC estimates that approximately 6.5% of the US adult population in 2021 had COPD and that there are likely more that have not been diagnosed and are not being treated. [d,3] Patients who experienced ≥3

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

exacerbations per year had a significantly reduced quality of life compared to patient with less frequent exacerbations.[4]

3.2. Description of Current Treatment Options

The aim of therapy is to improve patient symptoms, decrease exacerbations, and improve patient function and quality of life.[1]

Non-pharmacologic treatment includes cessation of smoking, and pulmonary rehabilitation. Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease.[5]

Inhaled therapy is the cornerstone of COPD treatment. The selection of initial treatment is based on the classification of severity (Grades A, B, and E). The following are classifications of treatment options for COPD:

- Short-acting beta agonist (SABA)
- Long-acting muscarinic agonist (SAMA)
- LAMA-Lon-acting beta agonist (LABA)
- Long-acting muscarinic agonist (LAMA)
- Inhaled corticosteroid (ICS)
- Combination products

Rescue bronchodilator therapy includes SABAs and SAMAs if the patient is not taking a LAMA. SABAs include albuterol and levalbuterol. Risks associated with SABAs include life-threatening paradoxical bronchospasms, the sign of deterioration of asthma and the requirement for reevaluation if the patient needs more doses than usual, the potential for inadequacy of monotherapy needing anti-inflammatory agents, cardiovascular effects, fatalities at higher than the recommended dose, immediate hypersensitivity reactions, caution with coexisting conditions such as cardiovascular disorders, convulsive disorders, hyperthyroidism, or diabetes mellitus, and hypokalemia.[6,7] SAMA includes ipratropium which is also available in combination with albuterol. Ipratropium risks include using for maintenance only and not acute episodes of bronchospasm, hypersensitivity reactions including anaphylaxis, paradoxical bronchospasm, ocular effects due to increased intraocular pressure, and urinary retention.[8] There are two products that combine a SABA and SAMA, albuterol and ipratropium taken with a Respimat, and albuterol and ipratropium taken with a nebulizer.[9,10]

Long-acting bronchodilator agents are recommended for patients with Group A symptoms and either a LABA or a LAMA is acceptable.[1] The decision to use one over another is based on patient response and preference (e.g., adverse drug events). LABA include salmeterol, arformoterol, formoterol, indacaterol, and olodaterol and all are beta-2 selective. Increase in asthma related deaths is considered a class effect of LABA and is a boxed warning in all LABA. Additional class wide warnings associated with LABAs are not to initiate in patients during deterioration of disease and acute episodes of asthma or COPD,

excessive use can result in an overdose, clinically significant cardiovascular effects and fatalities, paradoxical bronchospasm, immediate hypersensitivity reactions, caution in patients with certain coexisting conditions, hypokalemia, and hyperglycemia.[11] Salmeterol also includes drug interactions with strong cytochrome P450 3A4 inhibitors and that salmeterol is not a substitute for corticosteroids Salmeterol has a boxed warning for asthma-related deaths warning that monotherapy without inhaled corticosteroids increase the risk of asthma-related death. Use of salmeterol for the treatment of asthma as monotherapy without a concomitant ICS is contraindicated. The boxed warning also includes the increased risk of asthma-related hospitalization in pediatric and adolescent patients when LABA is used as monotherapy.[12]

LAMAs include tiotropium, aclidinium, and umeclidinium, glycopyrrolate, and revefenacin. There is no boxed warning for the LAMAs and the class wide warnings include that LAMAs are not intended for relief of acute symptoms, immediate hypersensitivity reactions, paradoxical bronchospasm, worsening of narrow-angle glaucoma, and worsening of urinary retention.[13] Tiotropium warnings also include the possibility for anticholinergic side effects in renal impairment.[14]

Inhaled corticosteroids include beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, and mometasone furoate. Although ICS used to be used along as part of COPD therapy, they are no longer recommended for use without accompanying long-acting bronchodilator therapy due to inhaled bronchodilators having greater benefit with fewer side effects.[1] ICS may be used in cases of asthma and COPD overlap.[15]

There are many combination products of the above-mentioned approved products, some of which include umeclidinium and vilanterol, olodaterol and tiotropium, indacaterol and glycopyrrolate, and glycopyrrolate and formoterol. The risks associated with combination products are the same as those of the individual compounds. Roflumilast is an oral PDE 4 inhibitor approved on February 28, 2011, indicated as chronic treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.[16] Roflumilast has no boxed warning, and the warnings and precautions include that roflumilast is not for use for the relief of acute bronchospasms, psychiatric events including suicidality, weight decrease, and drug interactions with strong cytochrome P450 enzyme inducers.

4. Benefit Assessment

The Applicant submitted data from two phase 3 clinical trials, Trial RPL554-CO-301 (Trial 301; NCT 04535986)) and Trial RPL554-CO-301 (Trial 302; NCT 03443414), as the primary support for the safety and efficacy of ensifentrine in COPD. Trial 301 was a multicenter, randomized (stratified based on background COPD medication usage), double blind, parallel-group, placebo-controlled trial to evaluate the efficacy and safety of ensifentrine 3 mg twice daily delivered by standard jet nebulizer compared to placebo in patients 40 to 80 years of age with moderate to severe COPD. There were several secondary endpoints including peak FEV_1 at week 12, weekly mean E-RS total symptom score at week 24, St. George's Respiratory Questionnaire (SGRQ) total score at week 24, morning trough FEV_1 at week 12, FEV_1 $AUC_{0\text{-}4h}$ at week 12, SGRQ responders at week 24 (defined as a change in ≥ -4 in total SGRQ score

from baseline). A total of 760 patients received study treatment and defined as the modified intention to treat (mITT) population. For the primary efficacy endpoint for Trial 301, change from baseline in the average FEV_1 $AUC_{0\text{-}12h}$ at Week 12, ensifentrine treatment demonstrated a statistically significant increase of 0.087 L compared to placebo (95% CI: 0.055, 0.118, p<0.0001) in the mITT population. The key secondary endpoints results were consistent with the primary endpoint findings with ensifentrine treatment demonstrating statistically significant improvements compared to placebo. [17]

Trial 302 has the same trial design as Trial 301 with the only difference is that Study 302 had a single cohort with a 24-week treatment period with no 48-week safety cohort. A total of 789 subjects received study treatment and were defined as the mITT population. For the primary efficacy endpoint, the change from baseline in the average FEV_1 $AUC_{0\text{-}12h}$ at Week 12, ensifentrine demonstrated a statistically significant increase of 0.094 L compared to placebo (95% CI: 0.067, 0.124, p<0.0001). Of the key secondary endpoints, only the peak FEV_1 at week 12 demonstrated a statistically significant difference between ensifentrine compared placebo.

The clinical reviewer concluded that treatment with ensifentrine 3 mg twice daily demonstrated improvement compared to placebo in the FEV_1 as measured by spirometry in the moderate to severe COPD population studied in Trials 301 and 302. The reviewer noted that the overall evaluation of the impact of ensifentrine on lung function as measured by spirometry in patients with moderate to severe COPD is favorable and are sufficient to support the benefit of ensifentrine 3 mg twice daily compared to placebo.[19, e]

5. Risk Assessment & Safe-Use Conditions

The safety of ensifentrine was based on the clinical data from Trial 301 and 302. In addition, the 24-week safety data from these trials were pooled for safety analysis.[18]

There were six deaths in the pooled 24-week safety database and three additional deaths occurred in the 48-week cohort of Trial 301 after the first 24 weeks. The clinical reviewer concluded that overall, the ensifentrine phase 3 studies had a low incidence of deaths and the deaths occurring in the phase 3 program did not raise any safety concerns.[19] The most common SAEs reported in the pooled analysis were COPD exacerbations, pneumonia and lung malignancies. The clinical reviewer determined that overall, the analysis of the SAEs did not raise any safety concerns.[19]

Trials 301 and 302 did not study Ohtuvayre in acute episodes of bronchospasm. Similar to all products approved for the maintenance treatment of COPD, the Prescribing Information (PI) will include that Ohtuvayre should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Ohtuvayre has not been studied in the relief of acute symptoms and extra doses of Ohtuvayre should not be used for that purpose. The safety and effectiveness of Ohtuvayre for relief of acute symptoms have not been established. Acute symptoms should be treated with an inhaled, short-acting bronchodilator.[19]

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5.1. Paradoxical Bronchospasm

Paradoxical bronchospasm is defined as the rapid onset of unexpected bronchospasm occurring shortly after the administration of an inhalation aerosol and it is unclear if one more etiology are responsible.[20] As with other approved inhalation products, Ohtuvayre will have a Warning and Precaution that as with other inhaled medicines, Ohtuvayre may produce paradoxical bronchospasm, which could be life threatening. The PI warns that if paradoxical bronchospasm occurs it should be immediately treated with an inhaled, short-acting bronchodilator and therapy should be immediately discontinued and alternative therapy instituted.

5.2. Psychiatric Events Including Suicidality

The 2021 National Survey on Drug Use and Health (NSDUH) reported that among adults aged 18 or older, 8.3% (or 21 million people) had a past year major depressive episode.[21,f] The National Center for Health Statistics Household Pulse Survey found that the range of average sub monthly percentages of US adults reporting symptoms of anxiety in April 2020- August 2021 was 28.2% - 37.2%.[22] In the Phase 3 program there was an increase in the baseline rates of depression (9.2% in Trial 301 and 22.4% in Trial 302) and anxiety (5.0% in Trial 301 and 17.9% in Trial 2). In the pooled database the most common reported adverse event related to psychiatric disorders was insomnia however there were no psychiatric safety signals identified where the 95% confidence interval excluded the null. The clinical reviewer notes that there does appear to be a numerical increase in the number of events in the Ohtuvayre group [1.2% (12/975) patients] compared to placebo [0.3% (2/597 patients].[19] Psychiatric events in the individual trials as well as the 48-week safety cohort were similar to the pooled analysis. There was 1 (0.1%) suicide attempt in the Ohtuvayre group in the phase 3 studies and 1 completed suicide in the phase 2 program.

Psychiatric disorders are included in the Warnings and Precautions of other PDE inhibitors including roflumilast which is also used to treat COPD. Similarly, Ohtuvayre will have a Warning and Precaution that treatment is associated with an increase is psychiatric adverse reactions, including suicidal ideation and behavior. Providers are advised to weigh the risk and benefit of treatment in patients with a history of depression and/or suicidal thoughts or behavior. The PI states that patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts, or other mood changes, and that if such changes occur to contact their healthcare providers.

6. Expected Postmarket Use

Ohtuvayre is most likely to be used both inpatient and outpatient on a chronic basis. Prescribers will most likely be both inpatient and office-based pulmonologists or primary care providers who are

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

familiar with the risks associated with other inhaled and oral products approved for the maintenance treatment of COPD. The drug will be self-administered by the patient and both the prescriber and patient will need to monitor for adverse events.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Ohtuvayre beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

In 2021, COPD was the sixth overall leading cause of death with approximately 6.5% of the US adult population diagnosed with COPD and likely more that have not been diagnosed and are not being treated. Ohtuvayre would be the first PDE3 and PDE4 inhibitor and has been proposed for the maintenance treatment of COPD in adult patients. The pivotal trials, Trials 301 and 302, support the efficacy of Ohtuvayre as evidenced by a statistically significant improvement in FEV_1 as measured by spirometry in the moderate to severe COPD population. The Clinical Reviewer recommends approval of Ohtuvayre on the basis of the efficacy and safety information currently available.

The risks associated with the use of Ohtuvayre are being used to treat acute symptoms of bronchospasm, paradoxical bronchospasm and psychiatric events including suicidality. The risk of maintenance products being used to treat acute symptoms of bronchospasm and paradoxical bronchospasm are included in all inhaled products approved for the treatment of COPD. Approved PDE3 inhibitors, including Daliresp which is approved for the maintenance treatment of COPD, include psychiatric events in the PI. These risks will be communicated in the Warnings and Precautions section of the PI with clear instructions to providers what to do if the patient experiences any of the risks associated with Ohtuvayre.

The likely prescribers are primary care providers and pulmonologists who are likely familiar with the risk of using Ohtuvayre to treat acute bronchospasms and the risk of paradoxical bronchospasms similar to other inhaled products. If a provider has prescribed a PDE3 inhibitor, including Daliresp, they are likely familiar with the risk of psychiatric events and the need to weigh the risks versus in benefit in treating patients with depression or suicidal thoughts or behaviors.

This reviewer has determined that a REMS is not necessary to ensure the benefits of Ohtuvayre outweigh its risks. The likely prescribers should have the knowledge and experience to diagnose, monitor, and manage these risks. The risks will be communicated through Warnings and Precautions section of labeling, and additional risk mitigation requirements are not necessary to maintain a favorable benefit-risk balance.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Ohtuvayre to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety

information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

Should Pulmonary, Allergy, and Critical Care have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

[1] Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease: 2024 Report. www.goldcopd.org (Accessed on April 1, 2024).

[2] American Lung Association. (2009, April 20). COPD Trends Brief. Lung disease. American Lung Association. Retrieved from https://www.lung.org/research/trends-in-lung-disease/copd-trends-brief

[3] Liu Y, Carlson S, Watson, K, et. al. Trends in the Prevalence of Chronic Obstructive Pulmonary Disease Among Adults Aged >18 years- United States, 2011–2021. Morbidity and Mortality Weekly Report. November 17, 2023;72(46);1250-1256.

[4] Seemungal T, Donaldson G, Paul E, et. al. Effects of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998; 157: 1418-1422.

[5] Rochester CL, Vogiatzis I, Holland AE, et. al. An Official American Thoracic Society/European Respiratory Society Policy Statement: Enhancing Implementation, Use, and Delivery of Pulmonary Rehabilitation. Am J Respir Crit Care Med. 2015 Dec;192(11):1373-86.

[6] Proair HFA label (albuterol) Prescribing Information. Teva Respiratory, LLC. Frazer, PA 19355. Last revised 02/25/2019. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021457s036lbl.pdf

[7] Xopenex label (levalbuterol) Prescribing Information. Last revised 2/27/2017. Sunovion Pharmaceuticals, Inc. Marlborough, MA 01752. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021730s039lbl.pdf

[8] Atrovent label (ipratropium) Prescribing Information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877. Last revised 01/10/2020. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021527s033lbl.pdf

[9] Combivent label (albuterol/ipratropium) Prescribing Information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877. Last revised 09/27/2020. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021747s020lbl.pdf

[10] Duoneb (albuterol/ipratropium) Prescribing Information. Dey Pharma, L.P. Napa, CA 94558. Last revised 05/29/2012. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020950s037lbl.pdf

[11] Brovana (arformoterol tartrate) Prescribing Information. Sunovion Pharmaceuticals Inc. Marlborough, MA 01752. Last revised 05/29/2019. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021912Orig1s032lblrpl.pdf

[12] Serevent (salmeterol) Prescribing Information. GlaxoSmithKline. Research Triangle Park, NC 27709. Last revised 07/22/2019. Accessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020692s047lbl.pdf

[13] Tudorza pressair (aclidinium bromide) Prescribing Information. AstraZeneca Pharmaceuticals LP. Wilmington DE 19803. Last revised 3/29/2019. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202450s012lbl.pdf

[14] Spiriva (tiotropium) Prescribing Information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877. Last revised 02/14/2019. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021936s012lbl.pdf

[15] Global Initiative for Asthma (GINA). Diagnosis and initial treatment of asthma, COPD, and asthma-COPD overlap: A joint project of GINA and GOLD updated April 2017. https://ginasthma.org/wp-content/uploads/2019/11/GINA-GOLD-2017-overlap-pocket-guide-wms-2017-ACO.pdf (Accessed on April 20, 2024).

[16] Daliresp (roflumilast) Prescribing Information. AstraZeneca Pharmaceuticals LP. Wilmington, DE 19850. Last revised 1/23/2018. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022522s009lbl.pdf

[17] Lennox, Alison. Clinical Review for Ohtuvayre (ensifentrine), 217389, accessed April 29, 2024.

[18] Verona Pharma, Inc. Summary of Clinical Safety for Ohtuvayre, June 26, 2023.

[19] Verona Pharma, Inc. Proposed Prescribing Information for Ohtuvayre, March 29, 2024.

[20] Cocchetto D, Sykes R, Spector S. Paradoxical Bronchospasm After Use of Inhalation Aerosols: A Review of the Literature. Journal of Asthma. 1991;28(1);49-53.

[21] The 2021 National Survey on Drug Use and Health (NSDUH) report. Rockville, Md.: Office of Applied Studies, Substance Abuse and Mental Health Services Administration, Dept. of Health & Human Services.

[22] National Center for Health Statistics Household Pulse Survey data on anxiety and depression collected between April 23, 2020, and Oct. 11, 2021. Available at www.cdc.gov/nchs/covid19/pulse/mental-health.htm

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LEAH M HART
06/12/2024 03:11:08 PM

CAROLYN N TIEU
06/12/2024 03:15:56 PM

CYNTHIA L LACIVITA
06/12/2024 03:22:58 PM