June 27, 2024

Noridian JA DME
Noridian JD DME
Attn: DME LCD Reconsiderations
900 42nd Street S
P.O. Box 6742
Fargo, ND 58103-6742

CGS JB DME
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Attn: Robert D. Hoover, Jr., MD, MPH
DME LCD Reconsiderations
26 Century Blvd., SET ST610
Nashville, TN 37214-3685

Delivered via email to: DMERecon@noridian.com and LCD ReconJC@cgsadmin.com

Dear Drs. Gurk & Hoover,

We are writing to formally request a reconsideration of your Final Local Coverage Determination #L33370 Nebulizers to incorporate coverage of Ohtuvayre (ensifentrine), inhalation suspension, the product described by HCPCS Code "*J76XX, Ensifentrine, inhalation suspension, FDA approved final product, non-compounded, administered through DME, unit dose form, 3 mg*". Medicare beneficiaries suffering with COPD should have access to this drug which has been shown in two Phase III clinical trials to be safe and to provide statistically significant improvement in baseline efficacy measurements. Based on guidance from CMS[1], CGS, and Noridian[2], below we detail the specific language changes we request for the Nebulizers LCD #L33370 and associated Policy Article #A52466 and provide the justification for such changes based on evidence in contemporaneous medical literature.

I. Background

Verona Pharma, Inc is a biopharmaceutical group focused on developing and commercializing innovative therapeutics for the treatment of respiratory diseases with significant unmet medical needs. Our product, Ohtuvayre (ensifentrine) inhalation suspension, is a first-in-class, inhaled, selective, dual inhibitor of the enzymes phosphodiesterase 3 and 4 ("PDE3" and "PDE4"), combining bronchodilator and non-steroidal anti-inflammatory activities in one compound.

In June 2023, we submitted a New Drug Application ("NDA")[3] #217389 to the U.S. Food and Drug Administration ("FDA") for approval of ensifentrine for the maintenance treatment of COPD. On June 26, 2024 the FDA approved Ohtuvayre for the maintenance treatment of chronic obstructive pulmonary disease in adult patients.[4]

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[1] *See* Medicare Program Integrity Manual, Chapter 13, Section 13.3; https://www.cms.gov/regulations-and-guidance/guidance/manuals/downloads/pim83c13.pdf
[2] *See* LCD Reconsideration Process, https://med.noridianmedicare.com/web/jddme/policies/lcd/reconsideration and https://www.cgsmedicare.com/jc/coverage/reconsideration.html
[3] *See* Attachment J for FDA Approval Correspondence
[4] *See* Attachment K for approved package insert

We are commercializing Ohtuvayre for the maintenance treatment of COPD in the United States. Ohtuvayre will be administered by patients, via a standard jet nebulizer.

II. Recommended LCD Language Changes

In light of the FDA approval of ensifentrine and contemporaneous medical literature supporting the use of ensifentrine in the COPD population we respectfully request that LCD #L33370 *Nebulizers* is reconsidered to address the following:

1. Section: Coverage Guidance, Coverage Indications, Limitations, and/or Medical Necessity is updated to include reference to ensifentrine. We recommend the following language (highlighted in red):

   a. It is reasonable and necessary to administer albuterol (J7611, J7613), arformoterol (J7605), budesonide (J7626), cromolyn (J7631), ensifentrine (J76XX), formoterol (J7606), ipratropium (J7644), levalbuterol (J7612, J7614), metaproterenol (J7669), or revefenacin (J7677) for the management of obstructive pulmonary disease (refer to the Group 8 Codes in the LCD-related Policy Article for applicable diagnoses); or

2. Consistent with FDA approval[5] and labeling[6], the Section: INHALATION DRUGS AND SOLUTIONS is updated to include a maximum allowable milligrams per month of ensifentrine. We recommend the following language in red:

   The following table represents the maximum milligrams/month of inhalation drugs that are reasonable and necessary for each nebulizer drug.

Inhalation Drugs and Solutions	Maximum Milligrams/Month
ensifentrine	180 mg/30 days (186 mg/31 days)

3. Section: INHALATION DRUGS AND SOLUTIONS is updated to include ensifentrine. We recommend the addition of the following language in red:

   Ensifentrine may be used alone or in addition to other bronchodilators (LAMA or LABA) and anti-inflammatory (ICS) inhaled therapies.

4. Section: Group 3 Paragraph: INHALATION DRUGS AND SOLUTIONS is updated to include ensifentrine. We recommend the following language in red:

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[5] *See* Attachment J for FDA Approval Correspondence

[6] *See* Attachment K for Full Package Insert

Group 3 Codes: (60 codes)

Code	Description
J76XX	ENSIFENTRINE inhalation suspension, FDA approved final product, non-compounded, administered through DME, unit dose form, 3 mg

We have included a full mark-up of the current policy at Attachment A for your reference.

III. Recommended Article Changes

With respect to the article "*Article – Nebulizers – Policy Article (A52466)*", we respectfully recommend the following changes (highlighted in red):

1. Section: INHALATION DRUGS

   The only FDA-approved unit dose preparation containing more than one drug is J7620, the combination of albuterol and ipratropium. Therefore, if the following FDA-approved unit dose codes are billed with a KP or KQ modifier, they will be rejected as invalid for claim submission: J7605, J7606, J2545, J7608, J7613, J7614, J7626, J7631, J7639, J7644, J7669, J7682, J7686, J76XX and Q4074.

2. Section: CODING INFORMATION

   Group 8 Paragraph:

   For HCPCS codes J7605, J7606, J7611, J7612, J7613, J7614 J7620, J7626, J7631, J7644, J7669, J7677, J76XX

We have included a full mark-up of the current billing article at Attachment L for your reference.

IV. Justification for Proposed Changes to Nebulizer LCD and Article

Medicare covers nebulizers and drugs administered through nebulizers as a treatment for COPD. Until recently nebulized COPD products were limited to bronchodilators (LAMA, LABA, SAMA, SABA) and anti-inflammatory (ICS) treatments. There is a significant body of evidence that has demonstrated the value inhibiting PDE for the treatment of COPD as evidenced by the use of theophylline and roflumilast in COPD, each limited by the plethora of adverse events.

Recently a growing body of evidence has demonstrated the value of phosphodiesterase (PDE) inhibitors in the treatment of COPD.

As early as 2000, researchers demonstrated that PDE inhibitors could be effective for the treatment of bronchial asthma and more specifically that PDE3 and PDE4 appear to effect human airways by directly relaxing airway muscles inhibiting mediator formation and release from inflammatory cells.[7] Studies demonstrated that PDE3 inhibition contributes to bronchodilation[8,9] while PDE4 inhibition affects airway inflammation and epithelial cell functions[10,11]. Dual inhibition of PDE3 and PDE4 may have additive or synergistic effects on bronchodilation and anti-inflammatory effects.[12]

Two phase 3 pivotal studies, ENHANCE-1[13] and ENHANCE-2[14] demonstrated ensifentrine's safety, tolerability and efficacy in the study populations as a nebulized formulation in adult patients with moderate to severe COPD.

In terms of peer reviewed published articles addressing the ENHANCE-1 and ENHANCE-2 trials, a summary of the pivotal publication is provided as follows:

Anzueto et al., *American Journal of Respiratory and Critical Care Medicine* 2023; *208*(4), 406-416. [15]

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[7] Schmidt DT, Watson N, Dent G, et al. The effect of selective and non-selective phosphodiesterase inhibitors on allergen- and leukotriene C(4)-induced contractions in passively sensitized human airways. *Br J Pharmacol*. 2000;131(8):1607-1618. doi:10.1038/sj.bjp.0703725

[8] Zuo H, Cattani-Cavalieri I, Valença SS, Musheshe N, Schmidt M. Function of cAMP scaffolds in obstructive lung disease: focus on epithelial-to-mesenchymal transition and oxidative stress. Br J Pharmacol. 2019;176(14):2402–2415. doi:10.1111/bph.1460535.

[9] Spina D, Page CP. Xanthines and phosphodiesterase inhibitors. Handb Exp Pharmacol. 2017;237:63–91

[10] Zuo H, Han B, Poppinga WJ, et al. Cigarette smoke up-regulates PDE3 and PDE4 to decrease cAMP in airway cells. Br J Pharmacol. 2018;175(14):2988–3006. doi:10.1111/bph.1434736.

[11] Milara J, Armengot M, Bañuls P, et al. Roflumilast N-oxide, a PDE4 inhibitor, improves cilia motility and ciliated human bronchial epithelial cells compromised by cigarette smoke in vitro. Br J Pharmacol. 2012;166(8):2243–2262. doi:10.1111/j.1476-5381.2012.01929.x39.

[12] Rabe KF, et al. *Am J Physiol.* 1993;264(5 Pt 1):L458-464. Schmidt DT, et al. *Br J Pharmacol.* 2000;131(8):1607-1618. Milara J, et al. *Clin Exp Allergy.* 2011;41(4):535-546. Giembycz MA, et al. *Br J Pharmacol.* 1996;118(8):1945-1958. Wright LC, et al. *Am J Physiol.* 1998;275(4):L694-700.)

[13] *See*: NCT04535986, A Phase 3 Clinical Trial to Evaluate the Safety and Efficacy of Ensifentrine in Patients With COPD

[14] *See*: NCT04542057, A Phase 3 Trial to Evaluate the Safety and Efficacy of Ensifentrine in Patients With COPD

[15] Anzueto A, Barjaktarevic I, Siler T, et al; ENHANCE investigators. Ensifentrine, a novel PDE3 and PDE4 inhibitor for the treatment of COPD: randomized, double-blind, placebo-controlled, multicenter, phase III trials (the ENHANCE trials). *Am J Respir Crit Care Med.* 2023;208(4):406-416.

These studies evaluated the effectiveness and safety of ensifentrine when compared to placebo for lung function, symptoms, quality of life and exacerbations in patients with COPD. The studies found that treatment with ensifentrine:

- Statistically significant and clinically meaningful improvements in lung function
- Improvements in symptoms and quality of life measures were shown in both trials
- Demonstrated adverse event rates similar to placebo

Specifically, both ENHANCE-1 and ENHANCE-2 were randomized, double-blind, parallel-group, placebo-controlled Phase 3 trials intended to provide replicate evidence of efficacy in terms of improvements in lung function, COPD symptoms and quality of life, and to demonstrate the safety of ensifentrine compared with placebo in patients with moderate to severe COPD. A total of 760 and 789 patients were randomized and treated in ENHANCE-1 and ENHANCE-2, respectively. Patients were randomized to ensifentrine 3 mg twice daily (BID) or placebo BID via a standard jet nebulizer. ENHANCE-1 included a 48-week subset to assess long-term safety.
Patients were stratified by trial duration (ENHANCE-1 only), background medication use, and smoking status.

The results of the ENHANCE-1 and ENHANCE-2 studies show that ensifentrine demonstrated evidence of bronchodilatory and nonsteroidal anti-inflammatory effects.

We believe this novel mechanism of action and clinical evidence supports the requested changes to the Nebulizers LCD to permit coverage of ensifentrine reported with HCPCS code J76XX. We have submitted an application for a permanent J-code for ensifentrine to the CMS HCPCS workgroup on June 27, 2024.

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V. CONCLUSION

Based upon the information we have provided, Verona believes that the use of OHTUVAYRE (ensifentrine) inhalation suspension (J76XX) to treat COPD is reasonable and necessary as demonstrated by its approval by the FDA and peer reviewed, published literature showing its efficacy, safety, and tolerability in this patient population. Thus the revisions requested to the LCD will ensure beneficiary access to this drug.

Thank you for the opportunity to submit this policy reconsideration. If there is additional information required to assist with your policy decision making, please do not hesitate to contact me or Matt Rysavy, Vice President Market Access and Trade at Matt.Rysavy@veronapharma.com.

Sincerely,

Kathleen Rickard, MD
Chief Medical Officer

Attachments

Attachment A: Redline LCD #33307 *Nebulizers*
Attachment B: Full copy of the peer-reviewed publication by Schmidt *et.al.,* 2000
Attachment C: Full copy of the peer-reviewed publication by Zuo *et.al.,* 2019
Attachment D: Full copy of the publication by Spina *et.al.,* 2017
Attachment E: Full copy of the peer-reviewed publication by Zuo *et.al.*, 2018
Attachment F: Full copy of the peer-reviewed publication by Milara *et.al.,* 2012
Attachment G: Full copy of the peer-reviewed publication by Singh *et.al.,* 2018
Attachment H: Full copy of the peer-reviewed publication by Ferguson *et.al.,* 2021
Attachment I: Full copy of the peer-reviewed publication by Anzueto *et.al.,* 2023
Attachment J: FDA Approval Correspondence
Attachment K: Full Package Insert
Attachment L: Redline Article #A52466 *Nebulizers – Policy Article*