PDL DRUG REVIEW

Proprietary Name: Ohtuvayre®
Common Name: ensifentrine
PDL Category: Phosphodiesterase Inhibitors

Comparable Products	Preferred Drug List Status
Roflumilast	Preferred with Conditions

Pharmacology/Usage: Ensifentrine, the active ingredient of Ohtuvayre®, is an inhibitor of phosphodiesterase 3 and 4 (PDE3 and PDE4). It is a small molecule that is an inhibitor of the PDE3 and PDE4 enzymes. PDE3 mainly hydrolyzes the second-messenger molecule cyclic adenosine monophosphate (cAMP) but is also capable of hydrolyzing cyclic guanosine monophosphate (cGMP). PDE4 hydrolyzes cAMP only. Inhibition of PDE3 and PDE4 results in accumulation of intracellular levels of cAMP and/or cGMP, resulting in various downstream signaling effects.

Indication: For the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adult patients.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Inhalation suspension in low-density polyethylene unit-dose ampules: 3mg/2.5ml (1.2mg/ml). Shake ampule vigorously before administration.

Recommended Dosage: Using a standard jet nebulizer equipped with a mouthpiece, inhale 3mg (one unit-dose ampule) twice daily, once in the morning and once in the evening, via oral inhalation.

Compatibility of Ohtuvayre® mixed with other drugs has not been established. Ohtuvayre® should not be physically mixed with other drugs or added to solutions containing other drugs.

Dosage adjustments are not required in patients with mild or moderate renal impairment. Patients with severe renal impairment have not been evaluated. Ensifentrine systemic exposure increased by 2.3-fold in subjects with moderate or severe hepatic impairment compared with healthy subjects. Use Ohtuvayre® with caution in patients with hepatic impairment.

Drug Interactions: There are no drug interactions listed with this product.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Ohtuvayre®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included back pain (0.8%), hypertension (0.8%), urinary tract infection (0.3%), and diarrhea (0.3%).

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 should not be used for that purpose. The safety and efficacy of Ohtuvayre® for relief of acute symptoms have not been established. Acute symptoms should be treated with an inhaled, short-acting bronchodilator.

As with other inhaled medicines, Ohtuvayre® may produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with Ohtuvayre®, it should be treated immediately with an inhaled, short-acting bronchodilator. Ohtuvayre® should be discontinued immediately and alternative therapy be started.

Treatment with Ohtuvayre® is associated with an increase in psychiatric adverse reactions. Psychiatric events including suicide-related adverse reactions were reported in clinical studies in patients who received Ohtuvayre®. Before starting treatment, healthcare providers should carefully weigh the risk and benefits of Ohtuvayre® treatment in patients with a history of depression and/or suicidal thoughts or behaviors. Healthcare providers should carefully assess the risks and benefits of continuing treatment with Ohtuvayre® if such events occur.

Contraindications: In patients with hypersensitivity to ensifentrine or any component of the product.

Manufacturer: Verona Pharma

Analysis: The efficacy of Ohtuvayre® was assessed in two 24-week randomized, double-blind, placebo-controlled, parallel-group clinical trials (ENHANCE-1 and ENHANCE-2) that enrolled adults (N=1553) with moderate to severe COPD.

ENHANCE-1 enrolled patients (N=763) randomized to receive 3mg Ohtuvayre® administered by oral inhalation via standard jet nebulizer such as PARI LC Sprint or placebo. Included participants had a mean age of 65 years (range 41 to 80), while 58% were male, 90% were white, 57% were current smokers, patients had a mean smoking history of 41 pack-years, and 25% reported exacerbations of COPD within the 15 months prior to the study. At screening, the mean post-bronchodilator percent predicted FEV1 was 52% and the mean post-bronchodilator FEV1/FVC ratio was 0.52. In addition, 68% were taking concurrent therapy: 30% taking concurrent LAMA, 18% taking concurrent LABA, and 20% taking concurrent LABA/ICS therapy throughout the trial.

ENHANCE-2 enrolled patients (N=790) randomized to receive 3mg Ohtuvayre® administered by oral inhalation via standard jet nebulizer such as PARI LC Sprint or placebo . Included participants had a mean age of 65 years (range 40 to 80), while 52% were female, 95% were white, 55% were current smokers, patients had a mean smoking history of 42 pack-years, and 21% of patients reported exacerbations of COPD within the 15 months prior to the study. At screening, the mean post-bronchodilator percent predicted FEV1 was 51%, and the mean post-bronchodilator FEV1/FVC ratio was 0.52. In addition, 55% of patients were taking concurrent therapy: 33% taking concurrent LAMA, 7% taking concurrent LABA, and 15% were taking concurrent LABA/ICS therapy throughout the trial.

The primary endpoint for both studies was the change from baseline in FEV1 AUC0-12h post dose at week 12. Results suggested that Ohtuvayre® demonstrated a statistically significant improvement in FEV1 AUC0-12h as compared to placebo in both studies. Results are presented in the table below, which was adapted from the prescribing information.

	ENHANCE-1		ENHANCE-2	
	Ohtuvayre® (N=479)	Placebo (N=284)	Ohtuvayre® (N=499)	Placebo (N=291)
n	477	282	498	291
Least Squares (LS) mean	61	-26	48	-46
LS mean difference from placebo	87	-	94	-

	ENHANCE-1		ENHANCE-2	
	Ohtuvayre® (N=479)	Placebo (N=284)	Ohtuvayre® (N=499)	Placebo (N=291)
p-value	<0.0001		<0.0001	

Trough FEV1 was defined as the last FEV1 value collected prior to the morning dose. The mean morning trough FEV1 improvement at week 12 relative to placebo was 35ml and 49ml in ENHANCE-1 and ENHANCE-2, respectively, which was statistically significant in ENHANCE-1 and not statistically significant in ENHANCE-2 due to failure higher in the testing hierarchy.

The St. George's Respiratory Questionnaire (SGRQ) was assessed in both studies. In ENHANCE-1, the SGRQ responder rate (defined as an improvement in score of 4 or more as threshold) for Ohtuvayre® at week 24 was 58.2% compared to 45.9% for placebo (OR 1.49). In ENHANCE-2, the SGRQ responder rate for Ohtuvayre® at week 24 was 45.4% compared to 50.3% for placebo (OR 0.92).

Place in Therapy: Ohtuvayre® is a phosphodiesterase 3 (PDE3) inhibitor and PDE4 inhibitor indicated for the maintenance treatment of COPD in adults that is to be administered by oral inhalation twice daily. The safety and efficacy of Ohtuvayre® were assessed in two randomized, double-blind, placebo-controlled trials that included adults with moderate to severe COPD. The primary endpoint for both studies was the change from baseline in FEV1 AUC0-12h post dose at week 12. In both trials, Ohtuvayre® demonstrated a statistically significant improvement in the primary endpoint as compared with placebo. Head-to-head active comparator trials were not currently found, but Ohtuvayre® offers providers and their patients with another treatment option.

Summary

There is no evidence at this time to support that Ohtuvayre® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Ohtuvayre® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Ohtuvayre [package insert]. Raleigh, NC: Verona Pharma, Inc; 2024.