A Report on Comparative Safety and Efficacy of Vilanterol in the treatment of Chronic Obstructive Pulmonary Disease (COPD)

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Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic progressive inflammatory lung disease that is characterized by persistent yet partially irreversible airflow limitation[1, 2]. Its symptomatic manifestations include dyspnea, chronic cough, and increased sputum production. COPD is currently one of the leading causes of death[3]. COPD is associated with a high morbidity and mortality rate and is currently a burden on society[4]. It has been estimated that by the year 2030, COPD will be the third leading cause of global mortality and will be directly responsible for 7.8% of all deaths[1]. Globally, chronic respiratory diseases are responsible for 6.3% of years lost due to disability, with COPD being the largest contributor. It makes up two-thirds of the global disability-adjusted life years[1].

To alleviate the symptoms, reduce the frequency and severity of exacerbations, and improve the health status are the goals of pharmacological therapy in COPD[5]. Long-acting inhaled bronchodilators are recommended as mainstay maintenance therapy for COPD in patients with moderate to severe symptoms[6]. These bronchodilators are categorized into two classes: long-acting muscarinic antagonists (LAMAs) and long-acting beta agonists (LABAs). Tiotropium is the once-daily LAMA, and the twice-daily LABAs include Salmeterol and Formoterol[7-9]. Muscarinic receptor antagonists inhibit hypersecretion of the mucous and relax the bronchial smooth muscles by reversing the cholinergic tone. They block the muscarinic type 1 receptor (M1) and muscarinic type 3 receptor (M3)[10-12]. The activation of the M2 autoreceptors, located in the pre-junction, inhibits excessive release of acetylcholine (ACh). Thus, blockade of M2 receptors increases ACh-mediated contractions[13-14]. Hence, anticholinergic drugs that

preferentially antagonize the M3 receptors should demonstrate improved efficacy compared with nonselective muscarinic receptor antagonists[15-16].

Revefenacin, a LAMA that has been designed to produce long-acting bronchodilation, with once-daily dosing and with a high degree of lung-selectivity[17-19]. It is the first and currently the only once-daily LAMA, nebulized bronchodilator to be approved for the treatment of chronic obstructive pulmonary disease (COPD). On 9th November 2018, based on the results of three phase III trials, the US Food and Drug Administration approved revefenacin[20]. It prevents bronchoconstriction by inhibiting muscarinic M3 receptors in the airway smooth muscles. The approved dosage of Revefenacin is 175 µg once daily and is delivered via a standard jet nebulizer connected to an air compressor[21]. LABA and LAMA improve airway patency and deflate the lungs[22].

Indacaterol (by Novartis), approved by USFDA in 2011, is the first once-daily LABA approved for treatment of COPD, and is administered by inhalation. The speed of bronchodilation is similar to that with Salbutamol (i.e., about five minutes) and longer (i.e., 24 hours) than that with traditional LABA, with the same 12-hour effect as Salmeterol and Formoterol, both of which require twice-daily administration. This is why Indacaterol has been called the “ultra-LABA”. On one hand, the fast onset of action provides immediate relief of symptoms, and on the other, its constant 24-hour bronchodilation provides “pharmacologic stenting” which facilitates lung emptying, thereby decreasing trapped gas and pulmonary hyperinflation. Once-daily administration of a fast and long-acting bronchodilator can improve patient adherence with therapy, which is known to be a major problem for many medical treatments[22]. Olodaterol (STRIVERDI RESPIMAT - Boehringer Ingelheim), approved by USFDA in 2014, is a long-acting beta$_2$ agonist (LABA) licensed for once-daily use as maintenance bronchodilator therapy for COPD[23].

The 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy recommends primarily the use of one long-acting bronchodilator [either a long-acting β_2-agonist (LABA) or a long-acting muscarinic antagonist (LAMA)] as the first-line therapy for patients with symptomatic COPD[24].

Vilanterol in combination with Fluticasone furoate (BREO ELLIPTA) was launched in the US in 2013 by GlaxoSmithKline for the maintenance treatment of airflow obstruction and for reducing exacerbations in patients with Chronic Obstructive Pulmonary Disease (COPD) in adults. Vilanterol (VI) is a long-acting beta$_2$-agonist (LABA) that binds to the beta$_2$-adrenoceptor on the airway smooth muscle, producing bronchodilation[25].

Pharmacokinetic data[25-27]

Innovator	GlaxoSmithKline (US – 2013)
Brand Name	BREO ELLIPTA (Fluticasone furoate + Vilanterol)
Regulatory Approval	USFDA - 2013
Patent Information (INH-IPM/Orange Book)	US – 21/05/2025, IND/CN – 11/09/2022, EU – 10/09/2027, JP – 04/09/2027, KR – 13/11/2025
Pregnancy Category	C
Dose & Dosage form	Inhalation powder – 25mcg - OD
ROA	Oral Inhalation
Approved Indications	Indicated for the maintenance treatment of airflow obstruction and for reducing exacerbations in patients with Chronic Obstructive Pulmonary Disease (COPD)
Indications under trial	Phase II: Asthma
Bioavailability	27.3%
Time to peak	Within 10 mins following inhalation
Protein binding	93.9%
Metabolism	Hepatic; CYP3A4
Elimination T½	21.3 hours
Excretion	Urine, Feces

Comparison of Safety[25, 28-32]

Parameter	Vilanterol	Olodaterol Hcl	Indacaterol	Revefenacin	Tiotropium	Formoterol
Adverse Effects	Nasopharyngitis – 10%; Headache – 9%; URTI - 5%; Oropharyngeal Candidiasis – 2%	Nasopharyngitis – 11.3%, URTI – 8.2%, Bronchitis – 4.7%, UTI – 2.5%, Cough – 4.2%, Back pain – 3.5%, Diarrhea – 2.9%, Dizziness – 2.3%, Rash – 2.2%, Arthralgia – 2.1%	Cough – 6.5%, Nasopharyngitis – 5.3%, Headache – 5.1%, Nausea – 2.4%, Oropharyngeal pain – 2.2%	Cough – 4%, Headache – 4%, Nasopharyngitis – 4%, URTI – 3%, Back pain – 2%	URTI – 41%, Sinusitis – 11%, Pharyngitis – 9%, Chest pain, UTI – 7%, Edema , Abdominal pain – 5%, Dry mouth – 16%, Dyspepsia, Rhinitis – 6%, Moniliasis, Epistaxis, Rash, Myalgia, Vomiting, Constipation – 4%	Nasopharyngitis, Dry mouth – 3.3%, Diarrhea, Nausea – 4.9%, Vomiting, Dizziness, Insomnia – 2.4%
Black Box Warning	Asthma related Death	Asthma related Death	Asthma related Death	Nil	Nil	Asthma related Death
Precautions	No Dosage adjustment is required in patients with hepatic or renal impairment.	No dosage adjustment is recommended in patients with mild-moderate hepatic and mild-moderate renal impairment.	No dosage adjustment is recommended in patients with mild-moderate hepatic impairment	No Dosage adjustment is required in patients with renal impairment.	Caution must be exerted for use in patients with renal impairment.	Pharmacokinetics not studied in subjects with hepatic or renal impairment.

Comparison of Efficacy[25, 28-32]

Outcome	Vilanterol	Olodaterol Hcl	Indacaterol	Revefenacin	Tiotropium	Formoterol
Mean change FEV_1 from Baseline (mL)	> 150 (Day 1) >150 (24 weeks)	110 (12 weeks)	190-220 (Day 1) 240-270 (12 weeks)	133 (Day 1) ~ 175 (12 weeks)	240 (Day 1) ~ 250 (24 weeks)	160 (12 weeks)
Mean FEV_1 Over Time (L)	-	1.4 (12 weeks)	>1.5 (12 weeks)	-	1.25 (Day 1) 1.3 (24 weeks)	1.55 (Day 1) 1.5 (12 weeks)

Conclusions

- Vilanterol in combination with Fluticasone furoate (BREO ELLIPTA) was launched in the US in 2013 by GlaxoSmithKline for the maintenance treatment of airflow obstruction and for reducing exacerbations in patients with Chronic Obstructive Pulmonary Disease (COPD) in adults. Vilanterol (VI) is a Long-Acting $Beta_2$-Agonist (LABA) that binds to the $beta_2$-adrenoceptor on the airway smooth muscle, producing bronchodilation.
- This comparison shows that, the efficacy in terms of Mean change FEV_1 from Baseline was greater with Tiotropium and Indacaterol.
- With regard to safety; like Olodaterol, Indacaterol, and Formoterol; Vilanterol also carries a black box warning for inducing Asthma related death. The adverse effects reported by Vilanterol were on a lower side and were

almost similar to that of Indacaterol. Further, Vilanterol is relatively safer in patients with hepatic or renal impairment.

- Towards the end, considering a great safety profile of the drug, it can be concluded that the overall safety vs. efficacy profile of Vilanterol is balanced for the treatment of COPD. However, it must be noted that this drug is approved only as a part of combination therapy with Fluticasone.

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