RXADVANCE
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CLINICAL UPDATE

Brand Name	Trelegy Ellipta®
Generic Name	fluticasone furoate/umeclidinium/vilanterol
Drug Manufacturer	GlaxoSmithKline

Clinical Update

TYPE OF CLINICAL UPDATE

New strength of 200/62.5/25 mcg and new indication for asthma

FDA APPROVAL DATE

September 9, 2020

LAUNCH DATE

Not available

REVIEW DESIGNATION

Not available

TYPE OF REVIEW

Efficacy; Labeling

DISPENSING RESTRICTIONS

Open Distribution

Overview

INDICATION(S) FOR USE

It is a combination of fluticasone furoate, an inhaled corticosteroid (ICS); umeclidinium, an anticholinergic; and vilanterol, a long-acting beta$_2$-adrenergic agonist (LABA), indicated for:

- The maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).
- The maintenance treatment of asthma in patients aged 18 years and older.

Limitations of use: Not indicated for relief of acute bronchospasm.

MECHANISMS OF ACTION

Trelegy Ellipta® contains fluticasone furoate, umeclidinium, and vilanterol.

Fluticasone Furoate

Fluticasone furoate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone furoate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is approximately 29.9 times that of dexamethasone and 1.7 times that of fluticasone propionate. The clinical relevance of these findings is unknown. The precise mechanism through which fluticasone furoate affects COPD symptoms is unknown. Inflammation is an important component in the pathogenesis of COPD. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, 17 Reference ID: 4433767 leukotrienes, cytokines) involved in

inflammation. Specific effects of fluticasone furoate demonstrated in in vitro and in vivo models included activation of the glucocorticoid response element, inhibition of pro-inflammatory transcription factors such as NFkB, and inhibition of antigen-induced lung eosinophilia in sensitized rats. These anti-inflammatory actions of corticosteroids may contribute to their efficacy.

Umeclidinium

Umeclidinium is a long-acting muscarinic antagonist, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical in vitro as well as in vivo studies, prevention of methacholine- and acetylcholine-induced bronchoconstrictive effects was dose-dependent and lasted longer than 24 hours. The clinical relevance of these findings is unknown. The bronchodilation following inhalation of umeclidinium is predominantly a site-specific effect.

Vilanterol

Vilanterol is a LABA. In vitro tests have shown the functional selectivity of vilanterol was similar to that of salmeterol. The clinical relevance of this in vitro finding is unknown. Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, there are also $beta_2$-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects. The pharmacologic effects of $beta_2$-adrenergic agonist drugs, including vilanterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

DOSAGE FORM(S) AND STRENGTH(S)

Inhalation powder: Inhaler containing 2 foil blister strips of powder formulation for oral inhalation. One strip contains fluticasone furoate 100 or 200 mcg per blister and the other contains umeclidinium/vilanterol 62.5 mcg/25 mcg per blister.

DOSE & ADMINISTRATION

Maintenance treatment of COPD: 1 actuation of 100/62.5/25 mcg once daily administered by oral inhalation

Maintenance treatment of asthma: 1 actuation of 100/62.5/25 mcg or 200/62.5/25 mcg once daily administered by oral inhalation

EFFICACY

The clinical efficacy of Trelegy Ellipta® has been evaluated in 3 clinical trials in subjects with COPD, including chronic bronchitis and/or emphysema: Trial 1 (NCT #01957163), Trial 2 (NCT #02119286), and Trial 3 (NCT #02164513). This led to original FDA approval.

Approval for new indication and strength was based on the CAPTAIN study. CAPTAIN (Clinical study of Asthma Patients receiving Triple therapy through A single INhaler) was a randomized, double-blind, active controlled, six-arm parallel group, global multicenter study evaluating FF/UMEC/VI (100/62.5/25 mcg, 200/62.5/25 mcg, 100/31.25/25 mcg, and 200/31.25/25 mcg) versus FF/VI (100/25 mcg and 200/25 mcg) given once-daily to patients whose asthma was inadequately controlled despite treatment with ICS/LABA (>250 mcg/day fluticasone propionate, or equivalent) maintenance asthma medication. In the study 2,436 patients were treated across 15 countries with approximately 400 patients randomly assigned to each of the six treatment arms.

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CAPTAIN evaluated as its primary endpoint the change from baseline in trough Forced Expiratory Volume in 1 second (FEV_1) at 24 weeks of treatment. The key secondary endpoint was the annualized rate of moderate/severe asthma exacerbations.

The study met its primary endpoint, demonstrating a statistically significant 110mL improvement in lung function (measured by change from baseline in trough FEV_1 at 24 weeks of treatment) for FF/UMEC/VI 100/62.5/25mcg ($p<0.001$, 95% CI: 66-153 mL) compared with Relvar/Breo 100/25 mcg and a statistically significant 92 mL improvement in trough FEV_1 for FF/UMEC/VI 200/62.5/25 mcg versus Relvar/Breo 200/25 mcg ($p<0.001$, 95% CI: 49-135 mL).

The key secondary endpoint was annualized rate of moderate/severe exacerbations for FF/UMEC/VI (100/62.5/25 mcg and 200/62.5/25 mcg) versus Relvar/Breo (100/25 and 200/25 mcg) and demonstrated a 13% (95% CI: -5.2 to 28.1) reduction in exacerbations, however this was not statistically significant.