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APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
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	209482
PDUFA Goal Date	September 18, 2017
OSE RCM #	2016-2842
Reviewer Name(s)	Laura Zendel, PharmD
Team Leader	Donella Fitzgerald, PharmD
Deputy Division Director	Jamie Wilkins Parker, PharmD
Review Completion Date	August 28, 2017
Subject	Evaluation of Need for a REMS
Established Name	Fluticasone furoate/Umeclidinium/Vilanterol
Trade Name	Trelegy Ellipta
Name of Sponsor	GlaxoSmithKline (GSK)
Therapeutic Class	Inhaled Corticosteroid/Long Acting Muscarinic Antagonist/Long Acting Beta Agonist
Formulation(s)	Inhalation Powder
Dosing Regimen	100/62.5/25 mcg oral inhalation once daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for Trelegy Ellipta (fluticasone furoate [FF]/ umeclidinium [UMEC]/ vilaterol [VI]) is necessary to ensure the benefits outweigh its risks. GlaxoSmithKline (GSK) submitted a New Drug Application (NDA 209482) for Trelegy Ellipta (FF/UMEC/VI) with the proposed indication for the long-term, once daily, maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. The Sponsor did not submit a REMS with this application but proposed proposed a risk management plan consisting of routine pharmacovigilance and risk minimization activities to address the risks of pneumonia, hypersensitivity, serious cardiovascular events, decreased bone mineral density, adrenal suppression, corticosteroid associated eye disorders, narrow angle glaucoma, bladder outlet obstruction, dysuria, urinary retention, paradoxical bronchospasm, serious asthma-related intubations and deaths in off label use in asthma, pregnancy and lactation, safety in long term use in COPD, and safety in severe hepatic impairment.

DRISK and the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) agree that a REMS is not needed to ensure the benefits of Trelegy Ellipta (FF/UMEC/VI) outweigh its risks. The safety concerns associated with FF/UMEC/VI use are well documented. In general, healthcare providers who treat COPD should be familiar with the risks associated with the use of inhaled corticosteroids, long acting muscarinic antagonists, long acting beta agonists, and combination inhalation products.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for Trelegy Ellipta (fluticasone furoate [FF]/ umeclidinium [UMEC]/ vilaterol [VI]) is necessary to ensure the benefits outweigh its risks. GlaxoSmithKline (GSK) submitted a New Drug Application (NDA 209482) for Trelegy Ellipta (FF/UMEC/VI) with the proposed indication for the long-term, once daily, maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). This application is under review in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). The sponsor did not submit a REMS with this application but proposed a risk management plan consisting of routine pharmacovigilance and risk minimization activities to address the risks of pneumonia, hypersensitivity, serious cardiovascular events, decreased bone mineral density, adrenal suppression, corticosteroid associated eye disorders, narrow angle glaucoma, bladder outlet obstruction, dysuria, urinary retention, paradoxical bronchospasm, serious asthma-related intubations and deaths, off label use in asthma, pregnancy and lactation, safety in long term use in COPD, and safety in severe hepatic impairment.

2 Background

2.1 PRODUCT INFORMATION

Trelegy Ellipta is a fixed dose combination of 100 mcg of fluticasone furoate (FF), an inhaled corticosteroid (ICS), 62.5 mcg of umeclidinium (UMEC), a long acting muscarinic antagonist (LAMA), and 25 mcg of vilanterol (VI), a long-acting beta agonist (LABA) administered by dry powder inhalation once daily. The Ellipta inhaler contains two strips; one containing a blend of micronized FF and lactose

monohydrate and the other containing a blend of micronized UMEC, micronized VI, magnesium stearate and lactose monohydrate. The inhaler will deliver, when actuated, the contents of a single blister simultaneously from each of the two strips. UMEC and VI are bronchodilators while FF has anti-inflammatory properties. The mechanism of action of UMEC is through inhibition of M3-receptors at the smooth muscle, while VI acts via beta-2 adrenergic receptors in the lungs and bronchial smooth muscle leading to bronchodilation. The precise mechanism through which FF affects COPD is not known, however inflammation is known to be an important component in the pathogenesis of COPD. Corticosteroids, such as FF, have been shown to have a wide range of action on multiple inflammatory cell types and mediators.

The proposed indication is for the long-term, once daily, maintenance treatment of patients with COPD. GSK's rationale for the development of an ICS/LAMA/LABA combination product is based on the established use of ICS, LAMA, and LABA therapeutic classes of drug as triple therapy to optimize disease management, particularly with increasing disease severity. GSK supports this treatment rationale using data demonstrating improvements in airflow obstruction and reductions in rescue albuterol with UMEC + FF/VI compared with FF/VI alone, and similar safety profiles for the two treatments. Presently, the availability of triple therapy for COPD requires the use of two or three separate inhalation products. Such treatment options may place a burden on patients due to the required use of multiple inhalers, potentially with different mechanisms for drug delivery and/or dosing frequency. The availability of FF/UMEC/VI in a single inhaler with once-daily administration has the potential to optimize COPD pharmacotherapy in appropriate patients that may benefit from triple therapy and also to improve patient adherence, convenience, and improve overall COPD disease management.

The combination product, Trelegy Ellipta (FF/UMEC/VI), is not currently approved in any jurisdiction, however, products containing the active ingredients are currently marketed in the United States, the European Union (EU) and multiple additional countries. Anoro Ellipta, a combination product containing UMEC/VI, was approved on 2/18/2013 for COPD. Breo Ellipta, a combination product containing FF/VI, was approved on 5/10/2013 for COPD and on 4/30/2015 for asthma. Incruse Ellipta, containing UMEC, was approved on 4/30/2014 for COPD. Arnuity Ellipta, containing FF, was approved on 8/20/2014 for Asthma.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 209482 relevant to this review:

- 2/24/2016: Approval of Supplement 2 to NDA 205382, Incruse Ellipta, to add the results of 4 studies evaluating the added bronchodilator benefit provided when UMEC is added to patients on background ICS/LABA therapy to the UMEC Prescribing Information
- 5/24/2016: DPARP informed the Sponsor it was reasonable to file an NDA application for a FF/UMEC/VI combination inhaler based on the results of studies 200109 and 200110 and in-vitro and pharmacokinetic data demonstrating the absence of pharmaceutical differences between the "closed triple" (FF/UMEC/VI) and "open triple" (FF/VI + UMEC)
- 11/18/2016: NDA 209482 submission for the long-term, once-daily, maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema received

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition[1,2]

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. The main risk factor for COPD is tobacco smoking, but other environmental exposures such as biomass fuel exposure and air pollution may contribute. Additional risk factors include genetic abnormalities, abnormal lung development, and accelerated aging. The most common symptoms include dyspnea and cough and/or sputum production. COPD may be punctuated by periods of acute worsening of respiratory symptoms or exacerbations. In 2014, COPD was the third leading cause of death in the United States.[3] In most patients, COPD is associated with significant concomitant chronic diseases, which increase its morbidity and mortality, and poor health-related quality of life.[4] It is estimated that by the year 2020, COPD will be the third leading cause of death worldwide.[5]

3.2 Description of Current Treatment Options

Pharmacological management of COPD is primarily aimed at improving symptoms and quality of life, optimizing lung function, reducing exacerbations, and improving exercise tolerance. Available therapies include smoking cessation, use of supplemental oxygen in the setting of chronic hypoxemia, and pharmacologic therapies including short and long acting bronchodilators, inhaled and systemic corticosteroids, theophylline and phosphodiesterase-4 inhibitors (see Table 1: Commonly Used Maintenance Medications in COPD). The use of combinations of drug classes with complementary mechanisms of action addresses the multi-component, inflammatory and progressive nature of COPD. According to the 2017 GOLD guidelines[1], the choice of therapeutic agent depends on the availability of medication and the patient's response and performance. As disease severity increases, COPD guidelines recommend an incremental approach to pharmacological treatment, involving the use of combinations of drug classes with different or complementary mechanisms of action.[1] Inhalation products include short acting and long acting bronchodilators, as well as combination products containing LAMA/LABA and ICS/LABA combinations. The combination use of the ICS, LAMA, and LABA therapeutic classes of drug as triple therapy can be used to optimize disease management, particularly with increasing disease severity.

4 Benefit Assessment

The clinical efficacy and safety of the combination of FF/UMEC/VI is supported by data from two pivitol phase 3 controlled studies, 200109 and 200110, demonstrating an additive lung function benefit when UMEC is added to background FF/VI therapy. Of note, studies 200109 and 200110 administered the triple therapy in an "open" configuration from two separate inhalers (FF/VI + UMEC) while this NDA application is for the approval of a "closed configuration" of FF/UMEC/VI in a single inhaler. GSK submitted adequate in-vitro and pharmacokinetic studies, CTT116415 and 200587, demonstrating a lack of pharmaceutical difference between FF/VI + UMEC and FF/UMEC/VI. These data support the conclusion that delivery into the lungs in terms of pharmaceutical performance, emitted dose, and

systemic exposure of all the componenents are comparable when administered as FF/UMEC/VI or UMEC + FF/VI.

200109 and 200110 were replicate randomized, double-blind, parallel group, placebo-controlled 12 week studies to evaluate the efficacy and safety of UMEC + FF/VI compared with placebo + FF/VI in subjects with moderate to very severe COPD. These studies were designed to evaluate improvement in airflow obstruction when UMEC is used in combination with FF/VI, supportive of the indication proposed for FF/UMEC/VI. Inclusion criteria included COPD diagnosis, $\geq$ 40 years of age, $\geq$ 10 pack-year history of smoking, pre and post bronchodilator forced expiratory volume in 1 second (FEV1)/ forced vital capacity (FVC) ratio < 0.70, and modified Medical Research Council (mMRC) dyspnea score $\geq$ 2. Exclusion criteria included clinically significant medical conditions as determined by the study investigator and other respiratory conditions such as a current history of asthma which could have confounded assessment of efficacy or safety. At the end of the run-in period, eligible subjects continued to receive open label FF/VI 100/25 mcg for four weeks. Patients were then randomized 1:1:1 to FF/VI 100/25 mcg + UMEC 62.5 mcg, FF/VI 100/25 mcg + UMEC 125 mcg, or FF/VI 100/25 mcg + Placebo. The primary endpoint was trough FEV1 on day 85. The secondary endpoint was 0-6 hr weighted mean (WM) FEV1 (day 84).

Results of 200109 and 200110

A combined total of 1238 patients were randomized in 200109 and 200110. The addition of both doses of UMEC + FF/VI resulted in statistically significant and clinically meaningful improvements in the primary endpoint of trough FEV1 at day 85 over placebo + FF/VI, however, no additional benefit was obtained with FF/VI + UMEC 125 mcg relative to FF/VI + UMEC 62.5 mcg. Treatment differences in trough FEV1 at day 85 for UMEC 62.5 mcg + FF/VI compared with placebo + FF/VI were 0.124 L (95% confidence interval [CI]: 0.093-0.154) in study 200109 and 0.122 L (95% CI: 0.118-0.187) in study 200100, p < 0.001 in both studies demonstrating an additive lung function benefit when UMEC is added to background FF/VI. Statistically and clinically meaningful improvements in the secondary endpoint were also demonstrated with both UMEC doses + FF/VI compared with placebo + FF/VI. Treatment differences at Day 84 for UMEC 62.5 mcg + FF/VI vs. placebo + FF/VI were 0.153 L (95% CI: 0.118-0.187) in study 200109 and 0.147 L (95% CI: 0.114-0.179) in study 200110, p < 0.001 in both studies.

5 Risk Assessment & Safe-Use Conditions

The pharmacologic effects of ICS, LABAs, and LAMAs in COPD are well characterized through extensive evaluation in the clinical development programs for approved ICS/LABA, LAMA, LABA, and LAMA/LABA products for COPD. Important risks related to ICS are pneumonia, decreased bone mineral density and associated fractures, adrenal suppression, and corticosteroid associated eye disorders. Important risks associated with antimuscarinics are serious cardiovascular events, narrow angle glaucoma, and bladder outlet obstruction, dysuria and urinary retention. Important risks associated with beta agonists are serious cardiovascular events and serious asthma-related intubations and deaths. Other important risks include paradoxical bronchospasm, hypersensitivity, and off label use in asthma, including pediatric use. Pharmacological class effects that are not included as important risks are hypokalemia, hyperglycemia, tremor, anticholinergic effects, and gastrointestinal obstruction. The clinical reviewer notes that no new

safety signals were identified from studies 200109 and 200110 that were not already known for FF/VI, UMEC/VI, and UMEC[6]. The frequency of non-fatal serious adverse events (SAEs) was similar across treatment arms (2-3%). The most commonly reported SAE was COPD with the highest incidence seen in the FF/VI + UMEC 125 mcg treatment arm (1%) compared to < 1% in the FF/VI + UMEC 62.5 mcg and FF/VI + placebo treatment arms.

No other non-fatal SAEs were reported with an incidence > 1%. The cardiovascular safety data from from studies 200109 and 200110 are not suggestive of any increased risk of cardiovascular events when UMEC is added to open-label FF/VI. Cardiovascular events occurred in 17 (4%) subjects in the FF/VI + placebo arm compared to 9 (2%) subjects in the FF/VI + UMEC 62.5 mcg arm and 8 (2%) subjects in the FF/VI + UMEC 125 mcg arm. Pneumonia and lower respiratory tract infection (LRTI) data are not suggestive of any increased risk of pneumonia or LRTI when UMEC is added to open-label FF/VI. Pneumonia occurred in 11 (1%) subjects in the FF/VI + placebo arm compared to 6 (<1%) subjects in the FF/VI + UMEC 62.5 mcg arm and 11 (1%) subjects in the FF/VI + UMEC 125 mcg arm. LRTI excluding pneumonia occurred in 5 (<1%) subjects in the FF/VI + placebo arm compared to 3 (<1%) subjects in the FF/VI + UMEC 62.5 mcg arm and 3 (<1%) subjects in the FF/VI + UMEC 125 mcg arm. Therefore, the safety profile of FF/UMEC/VI is consistent with known class effects of ICS, LABAs, and LAMAs, and ICS/LABA and LAMA/LABA combinations and indicates that FF/UMEC/VI can be safely administered to patients with COPD.

6 Expected Postmarket Use

Trelegy Ellipta (FF/UMEC/VI) is expected to be used at home or in an inpatient setting for daily COPD maintenance therapy. Each component in FF/UMEC/VI is approved either as a single entity or as a component in a dual combination product for the treatment of COPD.

7 Risk Management Activities Proposed by the Sponsor

The Sponsor proposes routine pharmacovigilance and labeling for Trelegy Ellipta (FF/UMEC/VI) . GSK states that routine risk minimization is achieved through contrainidications, limitations of use, warnings and precautions, and adverse event information communicated through the label and the patient information leaflet.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Trelegy Ellipta (FF/UMEC/VI) with the restricted indication for use in patients requiring additional bronchodilation on background FF/VI therapy on the basis of the efficacy and safety information currently available.

The clinical reviewer notes that the safety profiles for ICS, LABA and LAMA are well characterized in COPD. Each component in FF/UMEC/VI is approved either as a single entity or as a component in a dual combination product for the treatment of COPD. The safety profile of FF/UMEC/VI is consistent with

known class effects of ICS, LABAs, and LAMAs, and ICS/LABA and LAMA/LABA combinations and indicates that FF/UMEC/VI can be safely administered to patients with COPD. The prescribing information will contain a boxed warning outlining asthma-related death associated with LABAs and that Trelegy Ellipta is not indicated for the treatment of asthma. The Warnings and Precautions section will contain the same Warnings and Precautions for each of the three separate active ingredients and includes information about asthma-related deaths with use of LABAs, deterioration of disease and acute episodes, excessive use of Trelegy Ellipta and use with other LABAs, local effects of ICS, pneumonia, immunosuppression, transferring patients from systemic corticosteroid therapy, hypercorticism and adrenal suppression, drug interactions with strong cytochrome P450 3A4 inhibitors, paradoxical bronchospasm, hypersensitivity reactions including anaphylaxis, cardiovascular effects, reduction in bone mineral density, glaucoma and cataracts, worsening of narrow-angle glaucoma, worsening of urinary retention, coexisting conditions including convulsive disorders, thyrotoxicosis, diabetes mellitus and ketoacidosis, as well as hypokalemia and hyperglycemia. Additionally, a Medication Guide will be provided to further communicate the risks to patients. Therefore, the risks associated with FF/UMEC/VI will be communicated in the labeling.

Additionally, the clinical reviewer notes that this application does not formally address 21CFR300.50 (the Fixed-Combination Prescription Drug Rule) by providing clinical data demonstrating the clinical benefit provided by each component of the procuts, however, the data do support a restricted indication for use in patients requiring additional bronchodilation on background FF/VI therapy. Therefore, the approval of this single fixed-dose triple inhaler with a restricted incidation will provide patients requiring therapy with all three drug classes with a convenient treatment option while reflecting the efficacy data submitted in support of this application.

9 Conclusion & Recommendations

Based on the available data, it is the opinion of this reviewer that a REMS is not necessary to ensure the benefits outweigh the risks of pneumonia, hypersensitivity, serious cardiovascular events, decreased bone mineral density, adrenal suppression, corticosteroid associated eye disorders, narrow angle glaucoma, bladder outlet obstruction, dysuria, urinary retention, paradoxical bronchospasm, serious asthma-related intubations and deaths in off label use in asthma, pregnancy and lactation, safety in long term use in COPD, and safety in severe hepatic impairment. The safety concerns associated with FF/UMEC/VI use are well documented and consistent among other ICS/LAMA/LABA combination products. In general, healthcare providers who treat COPD should be familiar with the risks associated with the use of ICS, LAMAs, LABAs, and combination inhalation products.

Should DPARP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Materials Reviewed

The following is a list of materials informing this review:

1. GSK. Proposed Prescribing Information for Trelegy Ellipta, November 18, 2016.
2. GSK. Clinical Overview for Trelegy Ellipta, November 18, 2016.
3. GSK. US Risk Management Plan for Trelegy Ellipta, November 18, 2016.
4. Chaudhry, S. Division of Pulmonary and Rheumatoligy Products. Clinical Review for Trelegy Ellipta NDA 209482, August 14, 2017.

11 Appendices

11.1 Table 1: Commonly Used Maintenance Medications in COPD

Short Acting Beta Agonists (SABAs)			
Name (Year Approved) Generic	Dosing/Administration	Safety Issues	Risk Management Approach
Xopenex (1999), Xopenex HFA (2005) Levalbuterol	MDI: 45-90 mcg Neb: 0.31-0.63 mg Freq: every 6-8 hours	Paradoxical bronchospasm, not a substitute for corticosteroids, cardiovascular effects, need for more doses than usual may be a sign of deterioration and requires re-evaluation of treatment, excessive use may be fatal, hypersensitivity, hypokalemia, changes in blood glucose	Labeling
Proventil HFA (1996), Accuneb (2001), Ventolin HFA (2001), Vospire ER (2002) Proair HFA (2004), Proair Respiclick (2015) Albuterol	MDI: 90-180 mcg DPI: 90-180 mcg Neb: 0.63-1 25 mg Freq: every 4-6 hours Oral: 4-8mg extended release every 12 hours		Patient Information Sheet
Long Acting Beta Agonists (LABAs)			
Name (Year Approved) Generic	Dosing/Administration	Safety Issues	Risk Management Approach
Brovana (2006) aformoterol	Neb: 15 mcg every 12 hours	Increased risk of asthma-related death, contraindicated in asthma without use of a long-term asthma control medication, do not initiate in acutely deteriorating patients, do not use for relief of acute symptoms, excessive use can result in clinically significant cardiovascular effects and may be fatal, paradoxical bronchospasm can occur, caution in patients with cardiovascular or convulsive disorders, thyrotoxicosis or with sensitivity to sympathomimetic drugs	Medication Guide Boxed Warning
Foradil (2001), Foradil Certihaler (2006), Perforomist (2007) formoterol fumarate	DPI: 4.5-9 mcg Neb: 20 mcg Freq: every 12 hours		Medication Guide Boxed Warning
Arcapta Neohaler (2011) indacaterol maleate	DPI: 75 mcg every 24 hours		Medication Guide Boxed Warning
Striverdi Respimat (2014) olodaterol	SMI: 2.5 mcg two inhalations every 24 hours		Medication Guide Boxed Warning
Serevent (1994) Serevent Diskus (1997) salmeterol xinafoate	SMI: 25-50 mcg DPI: 50 mcg Freq: every 12 hours		Medication Guide Boxed Warning

Short Acting Anticholinergics (SAMAs)			
Name (Year Approved) Generic	Dosing/Administration	Safety Issues	Risk Management Approach
Atrovent HFA (2004) Ipratropium bromide	SMI: 17 mcg two inhalations four times per day up to 12 inhalations in 24 hours Neb: 0.2 mg/ml	Not indicated for the initial treatment of acute episodes of bronchospasm where rescue therapy is required for rapid response. Hypersensitivity reactions including anaphylaxis. Paradoxical bronchospasm. Use with caution in patients with narrow-angle glaucoma. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction due to urinary retention.	Labeling
Long Acting Anticholinergics (LAMAs)			
Name (Year Approved) Generic	Dosing/Administration	Safety Issues	Risk Management Approach
Tudorza Pressair (2012) aclidinium	DPI: 400 mcg every 12 hours	Not for acute use, not a rescue medication, paradoxical bronchospasm, worsening of narrow-angle glaucoma may occur, worsening of urinary retention may occur – caution in patients with prostatic hyperplasia or bladder-neck obstruction. May cause immediate hypersensitivity reactions (angioedema, bronchospasm or anaphylaxis) Use with caution in patients with severe hypersensitivity to milk proteins.	Labeling
Seebri (2015) Glycopyrrolate	DPI: 15.6 mcg every 12 hours		Labeling
Spiriva Handihaler (2004), Spiriva Respimat (2014) tiotropium bromide	DPI: 18 mcg SMI: 2.5 mcg Freq: every 24 hours		Labeling
Incruse Ellipta (2014) umeclidinium bromide	DPI: 62 5 mcg every 24 hours		Labeling
Combination SABA + SAMA			
Name (Year Approved) Generic	Dosing/Administration	Safety Issues	Risk Management Approach
Duoneb (2001) Combivent Respimat (2011) Albuterol; ipratropium	Neb: 3mg/0.5g SMI: 100/20 mcg Freq: every 6-8 hours	Hypersensitivity, paradoxical bronchospasm, cardiovascular effects, ocular effects (narrow-angle glaucoma), urinary retention, use with caution in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus	Labeling
Combination LABA + LAMA			
Name (Year Approved) Generic	Dosing/Administration	Safety Issues	Risk Management Approach
Bevespi Aerosphere (2016) Formoterol fumarate; glycopyrrolate	MDI: 9.6/14.4 mcg every 12 hours	All LABAs are contraindicated in patients with asthma without use of a long-term asthma controller medication – increased risk of asthma-related death. Do not initiate in acutely deteriorating COPD or to treat acute symptoms. Do not use in combination with an additional medicine containing a LABA because of risk of overdose. Discontinue if paradoxical bronchospasm occurs. Use with caution in patients with cardiovascular disorders, convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. May cause hypokalemia and hyperglycemia. Worsening of narrow-angle glaucoma may occur, worsening of urinary retention may occur – caution in patients with prostatic hyperplasia or bladder-neck obstruction	Medication Guide Boxed Warning
Utibron (2015) glycopyrrolate; indacaterol maleate	DPI: 27 5/15.6 every 12 hours		Boxed Warning
Anoro Ellipta (2013) umeclidinium bromide; vilanterol trifenatate	DPI: 25/62.5 mcg every 24 hours		Medication Guide Boxed Warning
Stiolto Respimat (2015) olodaterol hydrochloride; tiotropium bromide	SMI: 5/5 mcg every 24 hours		Boxed Warning

Combination ICS + LABA			
Name (Year Approved) Generic	Dosing/Administration	Safety Issues	Risk Management Approach
Symbicort (2006) budesonide; formoterol fumarate dihydrate	MDI: 4.5/160 mcg, 4.5/80 mcg two inhalations every 12 hours DPI: 9/320 mcg, 9/160 mcg every 12 hours	Asthma-related death: LABAs increase the risk. Prescribe only for recommended patient populations. Do not initiate in acutely deteriorating asthma or to treat acute symptoms. Do not use in combination with additional LABAs because of risk of overdose. Localized infections: candida albicans infection of the mouth and throat may occur; advise patients to rinse the mouth following inhalation. Immunosuppression: potential for worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infection or ocular herpes simplex infections, increased risk of pneumonia in COPD. Mor serious or even fatal course of chickenpox or measles can occur in susceptible patients. Risk of impaired adrenal function when transferring from oral steroids. Hypercorticism and adrenal suppression may occur with high dosages. Paradoxical bronchospasm. Caution in patients with cardiovascular disorders. Decreases in bone mineral density may occur. Monitor growth of pediatric patients. Monitor patients with change in vision or with a history of increased intraocular pressure, glaucoma and/or cataracts. Caution in patients with aneurysm, pheochromocytoma, convulsive disorders, thyrotoxicosis, diabetes mellitus and ketoacidosis. Monitor for hypokalemia and hyperglycemia.	Medication Guide Boxed Warning
Dulera (2010) formoterol fumarate; mometasone furoate	MDI: 5/100 mcg - 5/200 mcg two inhalations every 12 hours		Medication Guide Boxed Warning Note: FDA approved for asthma
Advair Diskus (2000), Advair HFA (2006) fluticasone propionate; salmeterol xinafoate	DPI: 5/100 mcg, 50/250 mcg, 5/500 mcg MDI: 21/45 mcg, 21/115 mcg, 21/230 mcg		Medication Guide Boxed Warning Note: Airduo (fluticasone propionate; salmeterol xinafoate) was approved in 2017 only for asthma
Breo Ellipta (2013) fluticasone furoate; vilanterol trifenatate	DPI: 25/100 mcg		Medication Guide Boxed Warning
Methylxanthines			
Name (Year Approved) Generic	Dosing/Administration	Safety Issues	Risk Management Approach
Elixophyllin (1979), Theocron (1985), Theo-24 (1983), Theophylline and Dextrose 5% in Plastic container (1984) Theophylline	Oral Elixir: 300-600 mg/day in divided doses every 6-8 hours Oral: 300-600 mg/day in divided doses every 6-8 hours, or every 12-24 hours for extended release formulations Inj: 0 3-0.4 mg/kg/hour up to 900mg/day	Use with caution due to increased risk of exacerbation of active peptic ulcer disease, seizure disorder, cardiac tachy-arrhythmias. The following conditions may reduce theophyllinc clearance and may require more intensive monitoring of serum theophylline concentrations: Age (< 1 year or > 60 years), acute pulmonary edema, congestive heart failure, cor-pulmonale, fever, hypothyroidism, liver disease, cirrhosis, acute hepatitis, sepsis with multi-organ failure, shock, cessation of smoking	Labeling
Phosphodiesterase-4 Inhibitors			
Name (Year Approved) Generic	Dosing/Administration	Safety Issues	Risk Management Approach
Dalirest (2011) Roflumilast	Oral: 500 mcg daily	Do not use for relief of acute bronchospasm, psychiatric events including suicidality, weight decrease, drug interactions: not recommended to use with strong CYP450 enzyme inducers (rifampicin, phenobarbital, carbamazepine, phenytoin)	Medication Guide

MDI = metered dose inhaler; DPI = Dry powder inhaler; SMI = soft mist inhaler; Neb = nebulizer; Inj = injectable

11.2 REFERENCES

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[2] Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systemic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380(9859): 2095-128

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[5] Mannino DM, Braman S. The epidemiology and economics of chronic obstructive pulmonary disease. Proc Am Thoracic Soc. 2007; 4:502-6

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