“Project IMPACT: Diabetes” Care Model Improves Health Outcomes in Underserved Populations in 25 Communities with a High Incidence of Diabetes

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Chronic disease is responsible for 7 of 10 deaths in the United States and 75% of the nation’s $2.2-trillion healthcare bill.3,4 According to the American Diabetes Association, nearly 26 million Americans have diabetes, and more than 200,000 die of this chronic disease annually. Patients with diabetes are at increased risk for diabetes-related complications, including heart disease, stroke, kidney failure, blindness, and lower-limb amputations.5

In 2010, the Bristol-Myers Squibb (BMS) Foundation announced the establishment of Together on Diabetes—a 5-year, $100-million initiative designed to improve the health outcomes of underserved patients with type 2 diabetes in the United States, China, and India.

One of the first 4 organizations in the BMS Foundation’s Together on Diabetes, the American Pharmacists Association (APhA) Foundation received a grant from the BMS Foundation to launch “Project IMPACT: Diabetes,” to bring quality care to underserved people in 25 US communities with a high incidence of diabetes.

Project IMPACT: Diabetes

The objectives of Project IMPACT: Diabetes are to expand the proven community-based model of care to patients who need it the most in communities across the United States, to improve key indicators of diabetes care in these selected communities, and to strengthen local models of care by establishing community peer-to-peer networking and mentoring relationships.

Organizations selected to participate in Project IMPACT: Diabetes include community and university-affiliated pharmacies, self-insured employers, federally qualified health centers, free health clinics, and others that have the opportunity to leverage unique stakeholders, existing programs, creative ideas, and additional resources to effectively adapt and implement similar models of care. The APhA Foundation also provides communities with tools, resources, guidance, and support to facilitate local success.

The APhA Foundation educates each community about this care model that places the patient with diabetes on the healthcare team, and inserts the pharmacist as a valued health coach. The Foundation also provides training and access to the Patient Self-Management Credential for Diabetes and a clinical data management tool, which are core components of the project.

The clinical data management tool standardized the data set that all 25 communities are collecting throughout the project. The APhA Foundation’s Patient Self-Management Credential for diabetes helps pharmacists identify the patient’s knowledge strengths and areas for improvement, allowing providers to customize the patient’s education and to address the biggest knowledge gaps first. Pharmacists are also able to use each patient’s credential level to recognize achievements in diabetes self-management knowledge, skills, and performance.

Through Project IMPACT: Diabetes, more than 2000 underserved patients, including those who are uninsured, underinsured, homeless, and/or living below the poverty line are currently receiving care from community-based interdisciplinary teams that include pharmacists, physicians, diabetes educators, and other healthcare professionals.

The cornerstone of local implementations is one-on-one patient consultations with pharmacists trained in diabetes care who monitor the patients’ A1c level, blood pressure, cholesterol, and body mass index, and help patients to manage their disease through appropriate medication use, exercise, nutrition, and other lifestyle changes. Pharmacists collaborate with and refer patients to physicians and other healthcare providers to ensure that patients receive comprehensive care.

In addition, the communities are encouraged to incentivize patients to stay motivated about diabetes self-management. Some incentives include bus passes,
Interim Results

Project IMPACT: Diabetes has scaled previous APhA Foundation collaborative care programs for the selected 25 communities. Over a mean duration of 6 months, healthcare teams saw statistically significant improvements in the diabetes-related clinical outcomes of their patients (Table), including an overall reduction in A₁c levels from 9.0% to 8.3%; a 7.3-mg/dL reduction in low-density lipoprotein cholesterol; and a 1.9-mm Hg reduction in systolic blood pressure. Dramatic improvements were also seen in patients’ ability to manage their diabetes, in large part as a result of the adaptability of the care model to fit local needs.

Conclusion

Every patient with diabetes faces challenges, such as adhering to prescribed medications, monitoring blood glucose levels, staying current with vaccines and foot and eye examinations, and maintaining a healthy diet and lifestyle. This initiative shows that all types of patients with diabetes, including the poor and uninsured, by working together with pharmacists and other members of the healthcare team, can be empowered to take the steps they need to understand and manage their diabetes. The interim results of Project IMPACT: Diabetes demonstrate that when patients are supported and empowered to make the lifestyle changes that are necessary to manage a chronic disease such as diabetes, significant improvements are possible. It is an idea whose time has come.

Author Disclosure Statement

Mr Bluml is an employee of the APhA Foundation.

References

Indications

• BREO ELLIPTA is a combination inhaled corticosteroid/long-acting beta_2-_agonist (ICS/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. BREO ELLIPTA is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.

• BREO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

Important Safety Information for BREO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

• Long-acting beta_2-_adrenergic agonists (LABAs), such as vilanterol, one of the active ingredients in BREO ELLIPTA, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including vilanterol.

• The safety and efficacy of BREO ELLIPTA in patients with asthma have not been established. BREO ELLIPTA is not indicated for the treatment of asthma.

CONTRAINDICATIONS

• BREO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to either fluticasone furoate, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

• BREO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.

• BREO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta_2-_agonist.

• BREO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

• Oropharyngeal candidiasis has occurred in patients treated with BREO ELLIPTA. Advise patients to rinse the mouth without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

• An increase in the incidence of pneumonia has been observed in subjects with COPD receiving BREO ELLIPTA. There was also an increased incidence of pneumonias resulting in hospitalization. In some incidences these pneumonia events were fatal.

– In replicate 12-month studies of 3255 subjects with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia reported in subjects receiving BREO ELLIPTA 100/25 mcg (6% [51 of 806 subjects]), fluticasone furoate (FF)/vilanterol (VI) 50/25 mcg (6% [48 of 820 subjects]), and FF/VI 200/25 mcg (7% [55 of 811 subjects]) than in subjects receiving VI 25 mcg (3% [27 of 818 subjects]). There was no fatal pneumonia in subjects receiving VI or FF/VI 50/25 mcg. There was fatal pneumonia in 1 subject receiving BREO ELLIPTA at the approved strength (100/25 mcg) and in 7 subjects receiving FF/VI 200/25 mcg (<1% for each treatment group).

• Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

• Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections.

• Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to BREO ELLIPTA.

• Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, discontinue BREO ELLIPTA slowly.
• Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections.

• Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as the clinical features may be atypical.

• BREO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of asthma.

• BREO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.

• BREO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated a history of exacerbations.

• BREO ELLIPTA is a combination inhaled corticosteroid/long-acting beta2-agonist (LABA).

• Indications

• BREO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

• An increase in the incidence of pneumonia has been observed in subjects with COPD receiving BREO ELLIPTA. There was also an increase in the incidence of bronchitis and sinusitis in subjects receiving BREO ELLIPTA compared to placebo.

• BREO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications that contain LABAs.

• CONTRAINDICATIONS

• Long-acting beta2-adrenergic agonists (LABAs) are contraindicated in patients with asthma-related death.

• The safety and efficacy of BREO ELLIPTA in patients with asthma have not been established. BREO ELLIPTA is not recommended for use in patients with asthma.

• Caution should be exercised when considering the coadministration of BREO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, neflinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.

• If paradoxical bronchospasm occurs, discontinue BREO ELLIPTA and institute alternative therapy.

• Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO ELLIPTA may need to be discontinued. BREO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

• Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO ELLIPTA and periodically thereafter.

• Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

• Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.

• Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

• The most common adverse reactions (≥3% and more common than placebo) reported in two 6-month clinical trials with BREO ELLIPTA (and placebo) were nasopharyngitis, 9% (8%); upper respiratory tract infection, 7% (3%); headache, 7% (5%); and oral candidiasis, 5% (2%).

• In addition to the events reported in the 6-month studies, adverse reactions occurring in ≥3% of the subjects treated with BREO ELLIPTA in two 1-year studies included COPD, back pain, pneumonia, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, hypertension, influenza, pharyngitis, diarrhea, peripheral edema, and pyrexia.

DRUG INTERACTIONS

• Caution should be exercised when considering the coadministration of BREO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, neflinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.

• BREO ELLIPTA should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists, such as vilanterol, on the cardiovascular system may be potentiated by these agents.

• Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may increase severe bronchospasm in patients with reversible obstructive airways disease.

• Use with caution in patients taking non–potassium-sparing diuretics, as electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists.

USE IN SPECIFIC POPULATIONS

• Use BREO ELLIPTA with caution in patients with moderate or severe hepatic impairment. Fluticasone furoate exposure may increase in these patients. Monitor for systemic corticosteroid effects.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for BREO ELLIPTA on the following pages.
BREO ELLIPTA\textsuperscript{\textregistered} (fluticasone furoate and vilanterol inhalation powder) FOR ORAL INHALATION USE

This is a brief summary only; see full prescribing information for complete product information

WARNING: ASTHMA-RELATED DEATH

Long-acting beta,-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the use of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol, an active ingredient in BREO ELLIPTA, has been established. BREO ELLIPTA is not indicated for the treatment of asthma.

1 INDICATIONS AND USAGE

BREO ELLIPTA is a combination inhaled corticosteroid/long-acting beta,-adrenergic agonist (ICS/LABA) indicated for the long-term, once-daily, maintenance treatment of airway obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. BREO ELLIPTA is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.

Important Limitations of Use: BREO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS

The use of BREO ELLIPTA is contraindicated in patients with severe hypersensitivity to any component of BREO ELLIPTA, including breathe right, short-acting beta2-agonist and vilanterol, or any of the excipients. [see Warnings and Precautions (5.11), Description (11) of full prescribing information].

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death

Data from a large placebo-controlled trial in subjects with COPD, back pain, pneumonia [see Warnings and Precautions (5.5)]

5.2 Deterioration of Disease and Acute Episodes

BREO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. BREO ELLIPTA has not been studied in patients with acutely deteriorating COPD. The initiation of BREO ELLIPTA in this setting is not appropriate.

5.3 Excessive Use of BREO ELLIPTA and Use With Other Long-Acting Beta,-Agonists

Breo Ellipta should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an alternative to long-acting LABA. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhalated sympathomimetic drugs. Patients using BREO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Potential Effect of Inhaled Corticosteroids

Local irritation of the mouth and pharynx with Candida albicans has occurred in subjects treated with BREO ELLIPTA. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREO ELLIPTA continues, but the use of antifungal therapy with BREO ELLIPTA may need to be interrupted. Advise the patient to rinse his/her mouth without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

5.5 Pneumonia

An increase in the incidence of pneumonia has been observed in subjects treated with another LABA (salmeterol). In clinical trials, the development of localized infections of the mouth and pharynx with Candida albicans has occurred in subjects treated with BREO ELLIPTA. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREO ELLIPTA continues, but the use of antifungal therapy with BREO ELLIPTA may need to be interrupted. Advise the patient to rinse his/her mouth without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

5.6 Use of Breo Ellipta in Patients with Asthma

BREO ELLIPTA is not indicated for the treatment of asthma.

5.7 Transferring Patients From Systemic Corticosteroid Therapy

Patients requiring oral corticosteroids for asthma should be instructed to discontinue the regular use of these drugs (range: 17% to 81%), indicating that the subject population had moderate to very severe COPD. Data are not available to determine whether the rate of death in patients with COPD related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in BREO ELLIPTA. Investigations have not been performed to determine whether oral corticosteroids should be instructed to resume oral corticosteroids in large doses immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplemental systemic corticosteroids during periods of stress or severe COPD exacerbation. Patients requiring oral corticosteroids should be monitored and treated with systemic corticosteroid effects. Particular care should be taken in observing patients with systemic corticosteroid effects. Particular care should be taken in observing patients with COPD, back pain, pneumonia [see Warnings and Precautions (5.5)]

5.8 Hypokalemia and Hyperglycemia

Asthma-Related Death

Data from a large placebo-controlled trial in subjects with COPD, back pain, pneumonia [see Warnings and Precautions (5.5)]

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

The electrocardiographic changes and/or QT prolongation were consistent with those seen with other LABAs and were not associated with clinically significant bradyarrhythmias. Because the QTc interval prolongation associated with vilanterol and fluticasone furoate was usually not associated with clinical symptoms of ventricular arrhythmias and recovery of hypothalamic-pituitary-adrenal (HPA) function. Patients who have been treated with systemic corticosteroids are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. If patients have had these diseases or beenproperly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IMIg) may be indicated. (See the respective package inserts for correct VZIG and IMIg dosage ). If chickenpox develops, treatment with antiviral agents may be considered. Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, systemic fungal, bacterial, viral, or parasitic infections, or ocular herpetic infections.

5.10 Paradoxical Bronchospasm

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

5.11 Hypersensitivity Reactions Hypersensitivity reactions may occur after administration of BREO ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not be treated with BREO ELLIPTA (see Contraindications) [4].

5.12 Cardiovascular Effects Viltalerol, like other beta2-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also in blood pressure. Such effects, such as supraventricular and ventricular extrasystoles, if such effects occur, BREO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of QT interval, and ST segment depression, although the clinical significance of these findings is unknown. In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12-fold higher systemic exposure than seen in patients with COPD) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO ELLIPITA, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias or hyperthyroidism.

5.13 Reduction in Bone Mineral Density Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term corticosteroids such as fracture is not known. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO ELLIPTA therapy. If significant reductions in BMD are seen and BREO ELLIPTA is still considered medically important for that patient’s COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered. In replicate 12-month trials in 3,255 subjects with COPD, bone fractures were reported by 2% of subjects receiving the fluticasone furoate/vilanterol combination (50 mcg/25 mcg: 2% [14 of 820 subjects]; 100 mcg/25 mcg: 2% [19 of 806 subjects]; or 200 mcg/25 mcg: 2% [14 of 811 subjects]) than in subjects receiving vilanterol 25 mcg alone (less than 1% [8 of 816 subjects]).

5.14 Glaucoma and Glaucoma-like Effects Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts. In replicate 12-month trials in 3,255 subjects with COPD, similar incidences of ocular effects (including glaucoma and cataracts) were reported in subjects receiving the fluticasone furoate/vilanterol combination (50 mcg/25 mcg: less than 1% [7 of 820 subjects]; 100 mcg/25 mcg: 1% [12 of 806 subjects]; 200 mcg/25 mcg: less than 1% [7 of 811 subjects]) as those receiving vilanterol 25 mcg alone (1% [9 of 816 subjects]).

5.15 Coexisting Conditions BREO ELLIPTA, like all medicines containing sympathomimetic agents, should be used with caution in patients with concomitant illnesses that may require supplementation with beta2-agonist medications may produce transient hyperglycemia in some patients. In clinical trials, 87% (55 of 811 subjects) of patients receiving vilanterol 25 mcg (3% [27 of 818 subjects]; 100 mcg 50 mcg: 2% [19 of 806 subjects]; or 200 mcg/25 mcg: 2% [14 of 811 subjects]) than in subjects receiving vilanterol 25 mcg alone (less than 1% [8 of 816 subjects]).

5.16 Hypokalemia and Hyperglycemia Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medications may produce transient hyperglycemia in some patients. In 4 clinical trials of 6- and 12-month duration evaluating BREO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium. 6 ADVERSE REACTIONS LABA, such as vilanterol, one of the active ingredients in BREO ELLIPTA, increase the risk of asthma-related death. BREO ELLIPTA is not indicated for the treatment of asthma. (See Boxed Warnings and Precautions (5.1).) Systemic and local corticosteroid use may result in the following: Increased risk of pneumonia in COPD (see Warnings and Precautions (5.8)), including the risk for decrease in bone mineral density (see Warnings and Precautions (5.13)).

6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The clinical program for BREO ELLIPTA included 7,700 subjects with COPD in two 6-month lung function trials, two 12-month exacerbation trials, and 6 other trials of shorter duration. A total of 2,428 subjects received vilanterol 25 mcg or fluticasone furoate/vilanterol 100 mcg/25 mcg, and 1,087 subjects have received higher doses of fluticasone furoate/vilanterol. The safety data described below are based on the confirmatory 6-month and 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.

6.2.6 Month Trials: The incidence of adverse reactions associated with BREO ELLIPTA in Table 1 is based on 2 placebo-controlled, 6-month clinical trials (Trials 1 and 2; n = 3,673). Of the 2,754 subjects, 70% were men and 84% were Caucasian. They had a median age of 62 years and an average smoking history of 44 pack years, with 54% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV1 was 48% (range: 14% to 87%), the mean postbronchodilator FVC/forced vital capacity (FVC) ratio was 47% (range: 17% to 88%), and the mean percent reversibility was 14% (range: -41% to 19%). Subjects received 1 inhalation once daily of the following: BREO ELLIPTA 100 mcg/25 mcg, fluticasone furoate/vilanterol 50 mcg/25 mcg, fluticasone furoate/vilanterol 200 mcg/25 mcg, fluticasone furoate 100 mcg, fluticasone furoate 200 mcg, vilanterol 25 mcg, or placebo.

Table 1. Adverse Reactions With ≥3% Incidence and More Common Than Placebo With BREO ELLIPTA in Subjects With Chronic Obstructive Pulmonary Disease

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>BREO ELLIPTA 100 mcg/25 mcg (n = 410)</th>
<th>Placebo 25 mcg (n = 408)</th>
<th>Vilanterol 100 mcg (n = 410)</th>
<th>Fluticasone Furoate 100 mcg (n = 410)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>9</td>
<td>10</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>7</td>
<td>9</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

*Includes terms oral candidiasis, oropharyngeal candidiasis, candidiasis, and oropharyngeal fungal.*

7 DRUG INTERACTIONS 7.1 Inhibitors of Cytochrome P450 3A4 Fluticasone furoate and vilanterol, the individual components of BREO ELLIPTA, are both substrates of CYP3A4. Concomitant administration of the potent CYP3A4 inhibitors ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of BREO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, treoleandomycin, voriconazole) (see Warnings and Precautions (5.9) and Clinical Pharmacology (12.3) of full prescribing information).

7.2 Monamine Oxidase Inhibitors and Tricyclic Antidepressants Viltalerol, like other beta-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta Adrenergic Receptor Blocking Agents Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of BREO ELLIPTA, but may produce severe bronchospasm in patients with reversible obstructive airflow obstruction. A profound cardiovascular response can occur in patients treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-blockers. For patients in whom these agents are used, beta-blockers should be used with caution.

7.4 Non-Potassium-Sparing Diuretics The electrocardiographic changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials with BREO ELLIPTA in pregnant women. Corticosteroids and beta2-agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal studies are not always predictive of human response, BREO ELLIPTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while...
taking BREO ELLIPTA. Fluticasone Furoate and Vilanterol: There was no evidence of teratogenic interactions between fluticasone furoate and vilanterol in rats at approximately 9 and 40 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mcg/m<sup>2</sup> basis at maternal inhaled doses of fluticasone furoate and vilanterol, alone or in combination, up to approximately 33,700 and 10,500 mcg/m<sup>2</sup>/day). Fluticasone Furoate: There were no teratogenic effects in rats and rabbits at approximately 9 and 2 times, respectively, the MRHDID in humans (on a mcg/m<sup>2</sup> basis at maternal inhaled doses up to 18 and 30 mcg/kg/day, respectively). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). Fetal skeletal variations included decreased ossification in the cervical vertebral centrum and metacarpals. There were no effects on perinatal and postnatal development in rats at approximately 3,900 times the MRHDID in humans (on a mcg/m<sup>2</sup> basis at maternal oral doses up to 10,000 mcg/kg/day).

Nursing Mothers: Human milk was not the only source of exposure to vilanterol, one of the active ingredients in BREO ELLIPTA, increase the risk of asthma-related death. Treatment with vilanterol, including in pregnancy, should only be used for those who have been adequately counselled on the potential benefits and risks of treatment. Patients with COPD who have received BREO ELLIPTA have a higher risk of pneumonia. Patients with COPD who have received BREO ELLIPTA have a higher risk of pneumonia and should be instructed to contact their healthcare providers if they develop symptoms of pneumonia (e.g., fever, chills, change in sputum color, increase in breathing problems).

8.3 Nursing Mothers: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 160 times, respectively, the MRHDID in adults (on a mcg/m<sup>2</sup> basis at maternal inhaled doses up to 33,700 and 10,500 mcg/m<sup>2</sup>/day). Fluticasone furoate and vilanterol exposure in subjects with severe renal impairment had no effect on vilanterol systemic exposure. Use BREO ELLIPTA with caution in patients with moderate or severe hepatic impairment. Monitor patients for cirrhosis-related side effects (see Clinical Pharmacology (12.3) of full prescribing information).

8.7 Renal Impairment: There were no significant increases in either fluticasone furoate or vilanterol exposure in subjects with severe renal impairment (CrCl<30 mL/min) compared with healthy subjects. No dosage adjustment is recommended. Avoid exposure to chickenpox or measles and if exposed, to consult their physicians without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or other herpetic simplex. Hypercorticism and Adrenal Suppression: Patients should be advised that BREO ELLIPTA may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk. GlaxoSmithKline was developed in collaboration with Theravance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: There were no significant increases in the in vivo micronuclear test in rats. No evidence of impairment of fertility was observed in male and female rats at inhaled fluticasone furoate doses up to 29 and 91 mcg/kg/day, respectively (approximately 3 and 9 times, respectively, the MRHDID in adults on an AUC basis). Vilanterol: In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulocystic adenomas in females at an inhalation dose of 29.500 mcg/kg/day (approximately 8,750 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mcg/kg/day (approximately 530 times the MRHDID in adults on an AUC basis). In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovanionaryomas in females and shortening of the latency of pituitary tumors at inhalation doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 45 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 2 times the MRHDID in adults on an AUC basis). These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonists drugs. The relevance of these findings to human use is unknown. Vilanterol tested negative in the following genotoxicity assays: in vitro bacterial (Ames assay) and in vivo mouse micronucleus assay, in vivo rat unscheduled DNA synthesis (UDS) assay, and in vitro Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the in vitro mouse lymphoma assay. There was no evidence of tumorigenic potential in male and female rats at inhaled vilanterol doses up to 3150 and 37,100 mcg/kg/day, respectively (approximately 12,000 and 14,000 times, respectively, the MRHDID in adults on a mcg/m<sup>2</sup> basis).

17.4 Risks Associated With Corticosteroid Therapy: Local Effects: Patients should be advised that localized infections with Candida albicans occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with BREO ELLIPTA, but at times therapy with BREO ELLIPTA may need to be temporarily interrupted under close medical supervision. Rinsing the mouth without swallowing after inhalation is advised to help reduce the risk of thrush. Pneumonia: Patients with COPD who have received BREO ELLIPTA have a higher risk of pneumonia and should be instructed to contact their healthcare providers if they develop symptoms of pneumonia (e.g., fever, chills, change in sputum color, increase in breathing problems).

17.1 Asthma-Related Death: In the 2-year inhalation studies in rats and mice at inhaled fluticasone furoate doses up to 9 and 19 mcg/kg/day, respectively (approximately equal to the MRHDID in adults on a mcg/m<sup>2</sup> basis), fluticasone furoate did not induce gene mutation in bacteria or chromosomal damage in a mammalian cell mutation test in mouse lymphoma L5178Y cells in vitro. There was also no evidence of genotoxicity in the in vivo micronuclear test in rats. No evidence of impairment of fertility was observed in male and female rats at inhaled fluticasone furoate doses up to 29 and 91 mcg/kg/day, respectively (approximately 3 and 9 times, respectively, the MRHDID in adults on an AUC basis).

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