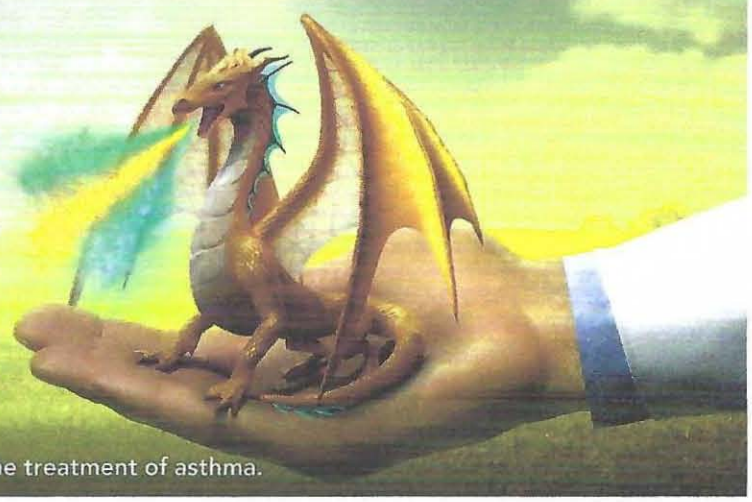
BREZTRI is indicated for the maintenance treatment of patients with chronic [illegible]monary disease (COPD).

RELEASE THE POWER OF PROTECTION WITH BREZTRI[1]



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BREZTRI is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

BREZTRI significantly reduced the annual rate of moderate or severe COPD exacerbations vs LAMA/LABA (RR=0.76; 95% CI: 0.69, 0.83; *P*<0.0001) and ICS/LABA (RR=0.87; 95% CI: 0.79, 0.95; *P*=0.0027).[1]* Annual rate estimate: BREZTRI 1.08; LAMA/LABA: 1.42; ICS/LABA 1.24.[1]

POWER TO PROTECT[1,2]

For patients with COPD and a recent history of exacerbations[1†]

In a 52-week study‡,
THE ONLY TRIPLE THERAPY‡ VS ICS/LABA TO SHOW A SIGNIFICANT REDUCTION IN COPD HOSPITALIZATIONS[2-4]

Hospitalization for a severe COPD exacerbation.*

16% reduction vs LAMA/LABA (RR=0.84; 95% CI: 0.69, 1.03; *P*=0.09)[2]

Annual rate estimate: BREZTRI 0.13 (n=2137); ICS/LABA 0.16 (n=2131); LAMA/LABA 0.15 (n=2120).[2]

STUDY 1[2,3]

20% REDUCTION VS ICS/LABA (rate ratio=0.80; 95% CI: 0.66, 0.97; *P*=0.02)[2§]

BREZTRI demonstrated a significant improvement in FEV_1 AUC_{0-4} vs ICS/LABA (116 mL; *P*<0.0001) and an improvement in mean change from baseline in morning pre-dose trough FEV_1 vs LAMA/LABA (13 mL; *P*=0.2375) at 24 weeks.[5]

POWER TO PREVENT[1,5]

For patients with COPD regardless of exacerbation history[1‖]

In a 24-week study where the majority of patients did not have a history of exacerbations within the last year,[6]
THE ONLY TRIPLE THERAPY‡ VS LAMA/LABA TO PREVENT MODERATE OR SEVERE EXACERBATIONS[1,4,5]*

18% reduction vs ICS/LABA (RR=0.82; 95% CI: 0.58, 1.17; *P*=0.2792)[1,5]

Annual rate estimate: BREZTRI 0.46 (n=639); LAMA/LABA 0.95 (n=625); ICS/LABA 0.56 (n=314).[5]

STUDY 2[1,5]

52% REDUCTION VS LAMA/LABA (rate ratio=0.48; 95% CI: 0.37, 0.64; unadjusted *P*<0.0001)[1,5¶]

See full study designs on the reverse.

*Moderate exacerbations were defined as those leading to treatment with systemic corticosteroids and/or antibiotics, and severe exacerbations were defined as those resulting in hospitalization or death.

†Patients with ≥1 moderate or severe exacerbation(s) in the year prior to screening.

‡Fixed-dose combination: ICS/LAMA/LABA.

§Based on predefined Type-1 error control plan.

‖Patients were not required to have a history of moderate or severe exacerbations in the year prior to screening.

¶*P* value is considered unadjusted due to nonsignificant results higher in the testing hierarchy.

- Most common adverse reactions (≥ 2%) associated with the use of BREZTRI in both studies included upper respiratory tract infection, pneumonia, dysphonia, muscle spasms, back pain, oral candidiasis, influenza, urinary tract infection, cough, sinusitis, and diarrhea[1]

BREZTRI is administered as 2 inhalations, twice daily[1]:

- Each inhalation delivers a combination of 160 mcg budesonide, 9 mcg glycopyrrolate, and 4.8 mcg formoterol fumarate

IMPORTANT SAFETY INFORMATION

- BREZTRI is contraindicated in patients who have a hypersensitivity to budesonide, glycopyrrolate, formoterol fumarate, or product excipients
- BREZTRI is not indicated for treatment of asthma. Long-acting $beta_2$-adrenergic agonist (LABA) monotherapy for asthma is associated with an increased risk of asthma-related death. These findings are considered a class effect of LABA monotherapy. When a LABA is used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone. Available data do not suggest an increased risk of death with use of LABA in patients with COPD

Please see additional Important Safety Information on reverse and accompanying full Prescribing Information, including Patient Information.

BREZTRI AEROSPHERE™
(budesonide 160 mcg, glycopyrrolate 9 mcg and formoterol fumarate 4.8 mcg) Inhalation Aerosol

IMPORTANT SAFETY INFORMATION (CONT'D)

- BREZTRI should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition
- BREZTRI is NOT a rescue inhaler. Do NOT use to relieve acute symptoms; treat with an inhaled short-acting beta$_2$-agonist
- BREZTRI should not be used more often than recommended; at higher doses than recommended; or in combination with LABA-containing medicines, due to risk of overdose. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs
- Oropharyngeal candidiasis has occurred in patients treated with orally inhaled drug products containing budesonide. Advise patients to rinse their mouths with water without swallowing after inhalation
- Lower respiratory tract infections, including pneumonia, have been reported following ICS. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap
- Due to possible immunosuppression, potential worsening of infections could occur. Use with caution. A more serious or fatal course of chickenpox or measles can occur in susceptible patients
- Particular care is needed for patients transferred from systemic corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients during and after transfer. Taper patients slowly from systemic corticosteroids if transferring to BREZTRI
- Hypercorticism and adrenal suppression may occur with regular or very high dosage in susceptible individuals. If such changes occur, consider appropriate therapy
- Caution should be exercised when considering the coadministration of BREZTRI with long-term ketoconazole and other known strong CYP3A4 Inhibitors. Adverse effects related to increased systemic exposure to budesonide may occur
- If paradoxical bronchospasm occurs, discontinue BREZTRI immediately and institute alternative therapy
- Anaphylaxis and other hypersensitivity reactions (eg, angioedema, urticaria or rash) have been reported. Discontinue and consider alternative therapy
- Use caution in patients with cardiovascular disorders, especially coronary insufficiency, as formoterol fumarate can produce a clinically significant cardiovascular effect 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
- Decreases in bone mineral density have been observed with long-term administration of ICS. Assess initially and periodically thereafter in patients at high risk for decreased bone mineral content
- Glaucoma and cataracts may occur with long-term use of ICS. Worsening of narrow-angle glaucoma may occur, so use with caution. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use BREZTRI long term. Instruct patients to contact a healthcare provider immediately if symptoms occur
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if symptoms occur
- Use caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis or unusually responsive to sympathomimetic amines
- Be alert to hypokalemia or hyperglycemia
- Most common adverse reactions in a 52-week trial (incidence ≥ 2%) were upper respiratory tract infection (5.7%), pneumonia (4.6%), back pain (3.1%), oral candidiasis (3.0%), influenza (2.9%), muscle spasms (2.8%), urinary tract infection (2.7%), cough (2.7%), sinusitis (2.6%), and diarrhea (2.1%). In a 24-week trial, adverse reactions (incidence ≥ 2%) were dysphonia (3.3%) and muscle spasms (3.3%)
- BREZTRI should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors and tricyclic antidepressants, as these may potentiate the effect of formoterol fumarate on the cardiovascular system
- BREZTRI should be administered with caution to patients being treated with:
  - Strong cytochrome P450 3A4 inhibitors (may cause systemic corticosteroid effects)
  - Adrenergic drugs (may potentiate effects of formoterol fumarate)
  - Xanthine derivatives, steroids, or non-potassium sparing diuretics (may potentiate hypokalemia and/or ECG changes)
  - Beta-blockers (may block bronchodilatory effects of beta-agonists and produce severe bronchospasm)
  - Anticholinergic-containing drugs (may interact additively). Avoid use with BREZTRI
- Use BREZTRI with caution in patients with hepatic impairment, as budesonide and formoterol fumarate systemic exposure may increase. Patients with severe hepatic disease should be closely monitored

Please see additional Important Safety Information on the front and accompanying full Prescribing Information, including Patient Information.

Study 1 Design: Study 1 was a 52-week, Phase 3, randomized, double-blind, parallel-group, multicenter study of 8588 patients with moderate to very severe COPD that compared BREZTRI MDI 320/18/9.6 (n=2157) with budesonide/glycopyrrolate/formoterol fumarate MDI 160/18/9.6 (n=2137), glycopyrrolate/formoterol fumarate MDI 18/9.6 (n=2143), and budesonide/formoterol fumarate MDI 320/9.6 (n=2151), each administered BID. Patients were current or former smokers with a smoking history of ≥10 pack-years, aged 40-80 years, with symptomatic COPD despite receiving 2 or more inhaled maintenance therapies, and a history of ≥1 moderate or severe exacerbation(s) in the previous year. The primary endpoint was the estimated annual rate of moderate or severe COPD exacerbations. Secondary endpoints included the estimated annual rate of severe COPD exacerbations.[1,2]

Study 2 Design: Study 2 was a 24-week, Phase 3, randomized, double-blind, parallel-group, multicenter study of 1896 patients with moderate to very severe COPD that compared BREZTRI MDI 320/18/9.6 (n=639) with glycopyrrolate/formoterol fumarate MDI 18/9.6 (n=625), budesonide/formoterol fumarate 320/9.6 (n=314), and budesonide/formoterol fumarate DPI 400/12 (n=318), each administered BID. Patients were current or former smokers with a smoking history of ≥10 pack-years, aged 40-80 years, with symptomatic COPD despite receiving 2 or more inhaled maintenance therapies. Patients were not required to have a history of moderate or severe exacerbations in the previous year. The primary endpoints were FEV_1 area under the curve from 0-4 hours (FEV_1 AUC_{0-4}) at Week 24 for BREZTRI compared to budesonide/formoterol fumarate and change from baseline in morning pre-dose trough FEV_1 at Week 24 for BREZTRI compared to glycopyrrolate/formoterol fumarate MDI. Secondary endpoints included the rate of moderate or severe COPD exacerbations.[1,5,6]

AUC=area under the curve; DPI=dry powder inhaler; FEV_1=forced expiratory volume in the first second; ICS=inhaled corticosteroids; LABA=long-acting beta$_2$-adrenergic agonist; LAMA=long-acting muscarinic antagonist; MDI=metered-dose inhaler; RR=rate ratio.

References: 1. BREZTRI AEROSPHERE [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020. **2.** Rabe KF, Martinez FJ, Ferguson GT, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med.* 2020;383(1):35-48. **3.** Data on File, REF-84029, AZPLP. **4.** Trelegy (fluticasone furoate, umeclidinium, and vilanterol inhalation powder) [package insert]. GSK group of companies, 2019. **5.** Ferguson GT, Rabe KF, Martinez FJ, et al. Appendix to: Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. *Lancet Respir Med.* 2018;6(10):747-758. **6.** Ferguson GT, Rabe KF, Martinez FJ, et al. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. *Lancet Respir Med.* 2018;6(10):747-758.

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BREZTRI
AEROSPHERE™
(budesonide, glycopyrrolate, and formoterol fumarate) Inhalation Aerosol