BREZTRI AEROSPHERE®

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

DESIGNED FOR PULMONOLOGISTS

BREZTRI is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

For your symptomatic patients with COPD,

WHAT IF YOU COULD HELP PREVENT THEIR NEXT EXACERBATION?

START PROTECTING WITH BREZTRI NOW

Fastest-growing fixed-dose triple therapy with Pulmonologists for the treatment of **COPD**[1]*

*Growth does not imply comparable efficacy, safety, or FDA-approved indications. Based on new-to-brand volume and share growth during the period from [July 2020 to April 2022]. Actual number of prescriptions was [244,400]. Source: IQVIA NPA-MD.

ETHOS: In Study 1 (52 weeks), BREZTRI significantly reduced the annual rate of moderate or severe COPD exacerbations vs LAMA/LABA (rate ratio=0.76; *P*<0.0001) and ICS/LABA (rate ratio=0.87; *P*=0.0027).[2,3] Annual rate estimate: BREZTRI 1.08; LAMA/LABA 1.42; ICS/LABA 1.24.[2,3]

KRONOS: In Study 2 (24 weeks), BREZTRI demonstrated a significant improvement in FEV_1 AUC_{0-4} vs ICS/LABA (116 mL; *P*<0.0001) and an improvement in change from baseline in morning pre-dose trough FEV_1 vs LAMA/LABA (13 mL; *P*=0.2375) at Week 24.[2,4]

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

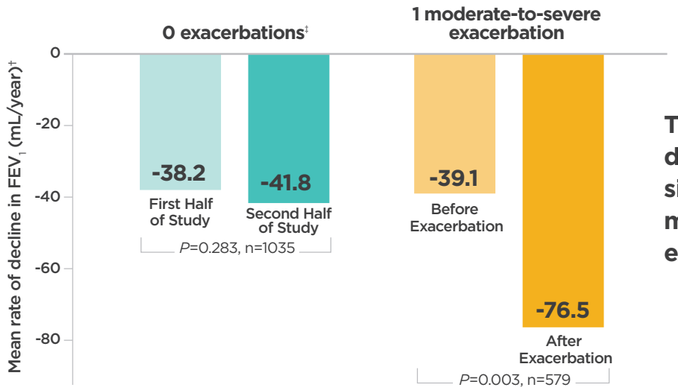
IMPORTANT SAFETY INFORMATION

- 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 throughout and accompanying full Prescribing Information, including Patient Information.

EVERY EXACERBATION CAN HAVE FAR-REACHING CONSEQUENCES FOR YOUR PATIENTS

1 exacerbation can lead to an accelerated decline in lung function[5*]



The rate of lung function decline increased significantly after a single moderate-to-severe exacerbation.

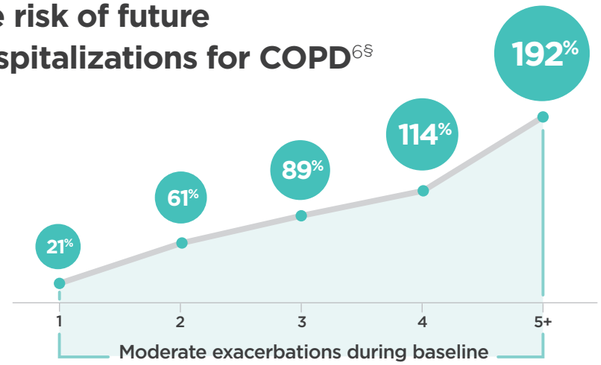
Adapted from Halpin DMG, Decramer M, Celli BR, Mueller A, Metzdorf M, Tashkin DP. Effect of a single exacerbation on decline in lung function in COPD. *Respir Med*. 2017;128:85-91. With permission from Elsevier.

*Retrospective analysis of annual rates of decline in FEV_1 before and after a single (and the only) moderate-to-severe exacerbation in patients during UPLIFT® (exacerbator subgroup n=586), compared with changes between the first and second half of the study in a non-exacerbator subgroup (n=1039). Moderate exacerbations were defined as those requiring treatment with an antibiotic or a systemic corticosteroid and severe as requiring hospitalization.

†Postbronchodilator.

‡Patients who did not experience an exacerbation during the UPLIFT® trial.

Exacerbations increased the risk of future hospitalizations for COPD[6§]



Patients with 1+ severe exacerbations during baseline had a

269%

greater risk of future hospitalization for COPD

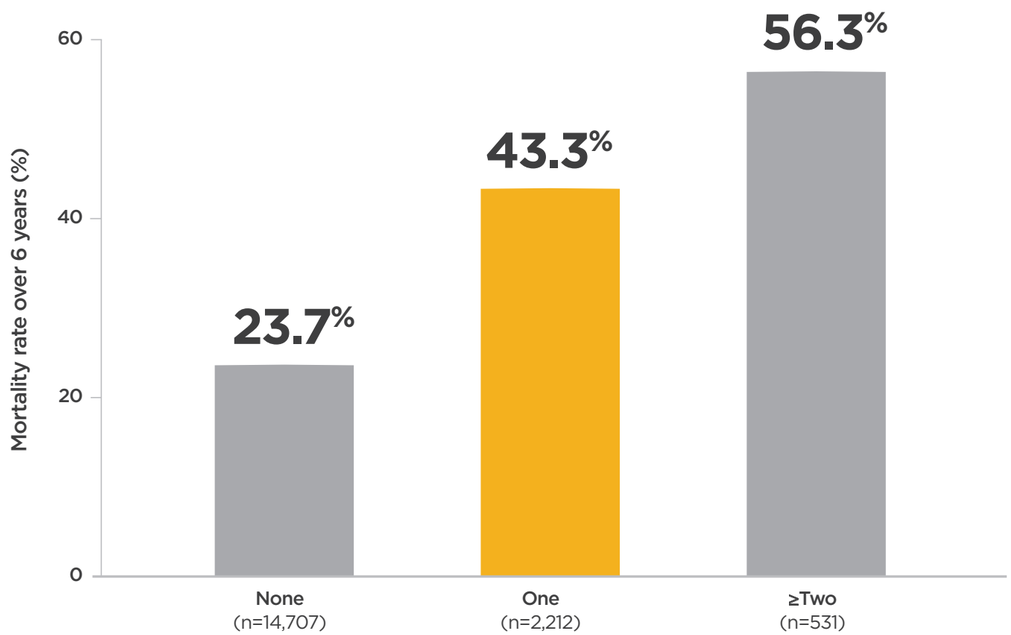
The increased rate of hospitalization for COPD is based on adjusted hazard ratios and was compared to patients who did not have an AECOPD during baseline.[§]

§Data from the UK Clinical Practice Research Datalink (population-based study) of ~100,000 patients with COPD investigating the effect of baseline AECOPD on future events with a follow up of up to 10 years. Moderate exacerbations were defined as those managed outside the hospital and severe as those requiring hospitalization. Hazard Ratios (adjusted for age, sex, smoking status, body mass index, comorbidities, and FEV_1 % predicted) for a future severe AECOPD are reported categorized by the number of exacerbations during baseline. Results provided as number of exacerbations during baseline; HR (95% CI): 0 Moderate; 1 (reference), 1 Moderate; 1.21 (1.14-1.27), 2 Moderate; 1.61 (1.52-1.72), 3 Moderate; 1.89 (1.76-2.03), 4 Moderate; 2.14 (1.95-2.35), 5+ Moderate; 2.92 (2.73-3.13), 1+ Severe; 3.69 (3.44-3.94).

SEVERE EXACERBATIONS LED TO HIGHER MORTALITY RATES[7‖]

43%

of patients died over the 6-year period after 1 hospitalization for COPD exacerbation



‖Cohort study evaluating whether severe COPD exacerbation frequency predicted mortality in 17,450 patients 18 years and older (only 6% were <40) in the Intermountain Healthcare system (US) from 2009 to 2014. Severe COPD exacerbations were defined as hospitalizations and/or ED visits for COPD exacerbations.

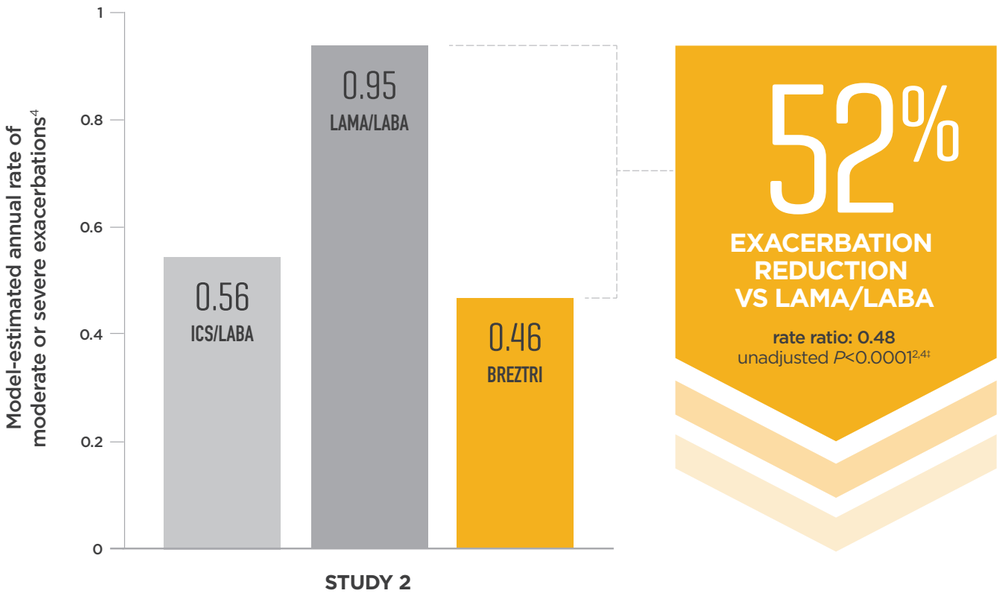
KRONOS—STUDY 2:

HOW WILL YOU HELP PROTECT YOUR PATIENTS FROM AN EXACERBATION?

For patients with COPD regardless of exacerbation history[2]*

In a 24-week study where the majority of patients did not have a history of exacerbations within the last year,[4]

BREZTRI was the ONLY triple therapy† vs LAMA/LABA to prevent moderate or severe exacerbations with a 52% reduction[2,4,8]



18% reduction vs ICS/LABA (rate ratio=0.82; *P*=0.2792)[2,4]

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

*Study 2: Patients (N=1902) were not required to have a history of moderate or severe exacerbations in the year prior to screening.
†Fixed-dose combination: ICS/LAMA/LABA.
‡*P* value is considered unadjusted due to nonsignificant results higher in the testing hierarchy.

IMPORTANT SAFETY INFORMATION (continued)

- 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.

MORE THAN 10,000 PATIENTS WITH VARIOUS SEVERITIES OF COPD WERE INCLUDED IN CLINICAL TRIALS[3,4]

KRONOS—STUDY 2[4]

74% of patients did not have a moderate or severe exacerbation in the previous 12 months

Baseline Characteristics	n, mITT	COPD severity, moderate/severe/ very severe, %	Postbronchodilator FEV_1, mean (SD), % predicted	Exacerbation history, 0 in past 12 months, % (moderate or severe)
BREZTRI MDI 320/18/9.6 mcg	**639**	**48.5 / 43.0 / 8.1**	**50.2 (14.3)**	**73.4**
GLY/FORM MDI 18/9.6 mcg	625	49.0 / 42.7 / 8.3	50.2 (13.8)	75.7
BUD/FORM MDI§ 320/9.6 mcg	314	49.0 / 42.4 / 8.3	50.0 (14.0)	74.8
BUD/FORM DPI‖ 400/12 mcg (open label)	318	50.3 / 43.4 / 6.3	50.7 (13.8)	73.6

- 71.8% of patients were receiving ICS-containing treatment at screening

ETHOS—STUDY 1[3]

57% of patients had experienced ≥2 moderate or severe exacerbations in the past 12 months

Baseline Characteristics	n, mITT	COPD severity, moderate/severe/ very severe, %	Postbronchodilator FEV_1, mean (SD), % predicted	Exacerbation history, 1/≥2 in past 12 months, % (moderate or severe)
BREZTRI MDI 320/18/9.6 mcg	**2137**	**28.7 / 61.1 / 10.2**	**43.6 (10.3)**	**44.0 / 55.9**
BUD/GLY/FORM MDI¶ 160/18/9.6 mcg	2121	28.5 / 59.9 / 11.6	43.1 (10.4)	43.9 / 56.0
GLY/FORM MDI 18/9.6 mcg	2120	28.1 / 61.0 / 10.8	43.5 (10.2)	42.8 / 57.1
BUD/FORM MDI§ 320/9.6 mcg	2131	28.8 / 60.2 / 10.9	43.4 (10.4)	42.8 / 57.1

- 21.2% of patients had experienced ≥1 severe exacerbation in the past 12 months
- 80.5% of patients were receiving an ICS-containing treatment at study entry

NOTE: All treatments were administered BID.
§BUD/FORM MDI delivered via the AEROSPHERE® inhaler is not an available product.
‖Not available in the US.
¶BUD/GLY/FORM 160/18/9.6mcg is not an approved dose.

IMPORTANT SAFETY INFORMATION (continued)

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

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ETHOS—STUDY 1

SEVERE EXACERBATIONS CAN NEGATIVELY AFFECT YOUR PATIENTS[2]

For patients with COPD and a recent history of exacerbations[2]*

In a 52-week study where patients had a history of exacerbations within the last year,[3†]

BREZTRI was the ONLY triple therapy[‡] vs ICS/LABA to show a significant reduction in severe exacerbations[3,8]

16% reduction vs LAMA/LABA (rate ratio: 0.84; *P*=0.09)[3]

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

*Study 1: Patients (N=8588) with ≥1 moderate or severe exacerbation(s) in the year prior to screening.
†Inclusive of a US population.
‡Fixed-dose combination: ICS/LAMA/LABA.
§Based on predefined Type-1 error control plan.

ETHOS—STUDY 1

DIFFERENCE OBSERVED IN TIME TO ALL-CAUSE MORTALITY (OVER 52 WEEKS)[9‖]

An observed relative difference with BREZTRI vs LAMA/LABA was shown in data published in 2020/2021, including in the *New England Journal of Medicine*[3,9]

SECONDARY ENDPOINT STUDY 1:
Time to all-cause mortality in the ITT population[9¶]

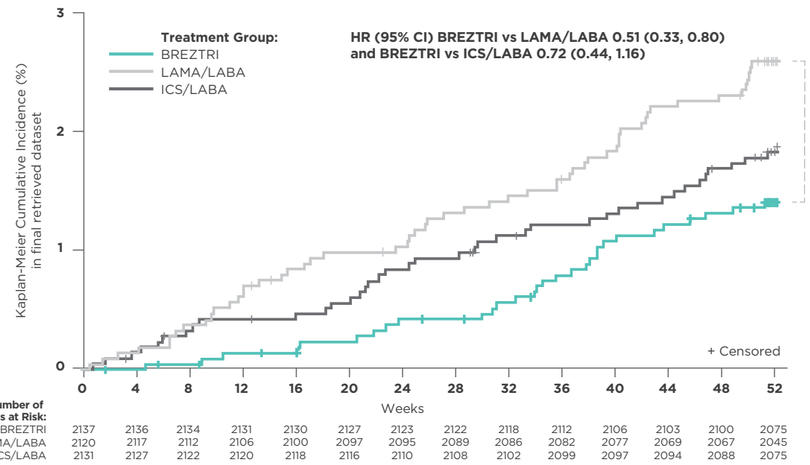

Figure adapted from Martinez FJ, et al. *Am J Respir Crit Care Med.* 2021;203(5):553–564.

49%
Observed relative difference with BREZTRI vs LAMA/LABA[9]

These results are observational in nature, and any comparisons between treatment arms should be interpreted with caution.

‖All-cause mortality was defined as death from any cause.
¶The analysis of time to death from any cause over 52 weeks was performed in the ITT population with the use of a treatment policy estimand, which included all observed data from the patients regardless of whether they continued to receive their assigned treatment.

IMPORTANT SAFETY INFORMATION (continued)

- 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

IMPORTANT SAFETY INFORMATION (continued)

- 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

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SAFETY PROFILE OBSERVED IN CLINICAL STUDIES[2]

In trials with more than 10,000 patients, BREZTRI had a safety profile comparable with LAMA/LABA and ICS/LABA.[2*]

Adverse reactions occurring at an incidence ≥2% of patients and more common in BREZTRI compared to LAMA/LABA and ICS/LABA (Study 1)

Adverse Reaction	BREZTRI 320/18/9.6 mcg n=2144 (%)	LAMA/LABA 18/9.6 mcg n=2125 (%)	ICS/LABA 320/9.6 mcg n=2136 (%)
Upper respiratory tract infection	123 (5.7)	102 (4.8)	115 (5.4)
Pneumonia	98 (4.6)	61 (2.9)	107 (5.0)
Back pain	67 (3.1)	55 (2.6)	64 (3.0)
Oral candidiasis	65 (3.0)	24 (1.1)	57 (2.7)
Influenza	63 (2.9)	42 (2.0)	61 (2.9)
Muscle spasms	60 (2.8)	19 (0.9)	53 (2.5)
Urinary tract infection	58 (2.7)	60 (2.8)	41 (1.9)
Cough	58 (2.7)	50 (2.4)	51 (2.4)
Sinusitis	56 (2.6)	47 (2.2)	55 (2.6)
Diarrhea	44 (2.1)	37 (1.7)	38 (1.8)

In 24-week data from Study 2, adverse reactions that occurred in patients treated with BREZTRI 320/18/9.6 mcg (n=639) at an incidence ≥2% included dysphonia (3.3%) and muscle spasms (3.3%).

*2783 patients with COPD received at least 1 dose of BREZTRI 320/18/9.6 mcg.

You are encouraged to report negative side effects of AstraZeneca prescription drugs by calling 1-800-236-9933. If you prefer to report these to the FDA, call 1-800-FDA-1088.

IMPORTANT SAFETY INFORMATION (continued)

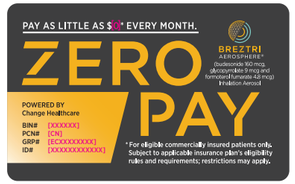
also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles

- 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

PRESCRIBE BREZTRI WITH CONFIDENCE IN COVERAGE

[Covered without prior authorization][†] for [8 out of 10] [Commercial and Medicare Part D] patients[‡] nationwide[10]

$0



[8 out of 10] commercially insured and eligible patients[§] can get BREZTRI for as low as $0 per month, every month.[10||]

[99.98%] of patients using BREZTRI ZERO PAY CARD paid [$0].[11¶]

[8 OUT OF 10]

BREZTRI [has] [preferred coverage[#]] for [8 out of 10] [Medicare Part D] patients.[10][**]]

[79%] of Medicare Part D patients pay [$50] or less a month out-of-pocket for their BREZTRI prescription.[11]

Individual costs and benefit design may vary by plan. Please consult with individual plans for specific information.

[†]"Without Prior Authorization" is defined as additional information is not required to be provided to the health plan in order for BREZTRI to be covered. Step edits may apply.
[‡]"Patients" is defined as covered lives [(Commercial, EGWP, Employer, Fed Prog, FEHBP, HIX, Medicare MA, Medicare, PDP, Medicare SN, Medi-Medi, Municipal Plan, PACE, PBM, Pvt HIX, Union)] at [Tiers 1-7] in the nation, as calculated by Fingertip Formulary® as of [10/18/2022].
[§]"Patients" is defined as covered lives [(Commercial, Employer, Fed Prog, FEHBP, HIX, Municipal Plan, PBM, Pvt HIX, Union)] at [Tiers 1-7] in the nation, as calculated by Fingertip Formulary® as of [10/18/2022].
[||]For commercially insured patients. [Subject to eligibility and monthly savings limit.] [Restrictions apply.]
[¶]Commercially insured/covered patients with no restrictions (step-edit, prior authorization, or NDC block).
[#]"Preferred Coverage" is defined as Tier 1, Tier 2, or Tier 3 when Tier 3 is the lowest branded tier.
[**]"Patients" is defined as covered lives [(EGWP, Medicare MA, Medicare PDP, Medicare SN, Medi-Medi, PACE)] [at Tiers 1–3 Preferred] in the nation, as calculated by Fingertip Formulary® as of [10/18/2022].

IMPORTANT SAFETY INFORMATION (continued)

- Use caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis or unusually responsive to sympathomimetic amines
- Be alert to hypokalemia or hyperglycemia

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STUDY DESIGNS

ETHOS[3]

Study 1 design: 52-week, Phase 3, randomized 1:1:1:1, double-blind, multicenter, parallel-group trial of 8588 patients with moderate to very severe COPD, comparing BREZTRI MDI 320/18/9.6 mcg (n=2157), BUD/GLY/FORM MDI 160/18/9.6 mcg (n=2137), GLY/FORM MDI 18/9.6 mcg (n=2143), and BUD/FORM MDI 320/9.6 mcg (n=2151), each administered BID. Patients were 40-80 years of age, smoking history of ≥10 pack-years, symptomatic COPD while receiving ≥2 inhaled maintenance therapies, and had a history of ≥1 moderate or severe exacerbation(s) in the previous year. The primary endpoint was the annual rate of moderate or severe COPD exacerbations, and secondary endpoints included the annual rate of severe COPD exacerbations and time to death (all cause). Moderate exacerbations were defined as those leading to treatment with systemic corticosteroids and/or antibiotics, and severe exacerbations as those resulting in hospitalization or death.

KRONOS[4]

Study 2 design: 24-week, Phase 3, randomized 2:2:1:1, double-blind, multicenter, parallel-group trial of 1902 patients with moderate to very severe COPD, comparing BREZTRI MDI 320/18/9.6 mcg (n=640), GLY/FORM MDI 18/9.6 mcg (n=627), BUD/FORM MDI 320/9.6 mcg (n=316), and open-label BUD/FORM DPI 400/12 mcg (n=319), each administered BID. Patients were 40-80 years of age, smoking history of ≥10 pack-years, symptomatic COPD while receiving ≥2 inhaled maintenance therapies with no requirement for a moderate or severe exacerbation(s) in the previous year. Primary endpoints were FEV_1 AUC_{0-4} for BREZTRI vs BUD/FORM MDI and change from baseline in morning pre-dose trough FEV_1 for BREZTRI vs GLY/FORM MDI at Week 24. Secondary endpoints included the rate of moderate or severe COPD exacerbations. Moderate exacerbations were defined as those leading to treatment with systemic corticosteroids and/or antibiotics, and severe exacerbations as those resulting in hospitalization or death.

References

1. Data on File, US-69687, AZPLP. **2.** BREZTRI AEROSPHERE [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2021. **3.** Rabe KF, Martinez FJ, Ferguson GT, et al; ETHOS Investigators. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD [article and supplementary appendix]. *N Engl J Med*. 2020;383(1):35-48. **4.** 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 [article and supplementary appendix]. *Lancet Respir Med*. 2018;6(10):747-758. **5.** Halpin DMG, Decramer M, Celli BR, Mueller A, Metzdorf N, Tashkin DP. COPDGene Investigators. Effect of single exacerbation on decline in lung function in COPD. *Respir Med*. 2017;128:85-91. **6.** Rothnie KJ, Müllerová H, Smeeth L, Quint JK. Natural history of chronic obstructive pulmonary disease exacerbations in a general practice-based population with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2018;198(4):464-471. **7.** Blagev D, Collingridge DS, Rea S, et al. Stability of frequency of severe chronic obstructive pulmonary disease exacerbations and health care utilization in clinical populations. *Chronic Obstr Pulm Dis*. 2018;5(3):208-220. **8.** Trelegy (fluticasone furoate, umeclidinium, and vilanterol inhalation powder) [package insert]. GSK group of companies, 2022. **9.** Martinez FJ, Rabe KF, Ferguson GT, et al. Reduced all-cause mortality in the ETHOS trial of budesonide/glycopyrrolate/formoterol for chronic obstructive pulmonary disease: a randomized, double-blind, multi-center, parallel-group study. *Am J Respir Crit Care Med*. 2021;203(5):553-564. **10.** Formulary Data are provided by Fingertip Formulary® and are current as of [10/18/2022]. **11.** [Data on File, REF-69326, AZPLP.]

Abbreviations

AECOPD=Acute exacerbations of chronic obstructive pulmonary disease, **AUC_{0-4}**=area under the curve from 0-4 hours, **BID**=twice daily, **BUD**=budesonide, **COPD**=chronic obstructive pulmonary disease, **DPI**=dry powder inhaler, **ED**=emergency department, **FEV_1**=forced expiratory volume in 1 second, **FORM**=formoterol fumarate, **GLY**=glycopyrrolate, **ICS**=inhaled corticosteroid, **ITT**=intent-to-treat, **LABA**=long-acting $beta_2$-adrenergic agonist, **LAMA**=long-acting muscarinic antagonist, **mITT**=modified intent-to-treat, **MDI**=metered dose inhaler, **SD**=standard deviation.

IMPORTANT SAFETY INFORMATION (continued)

- 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

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

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
- 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 accompanying full Prescribing Information, including Patient Information.

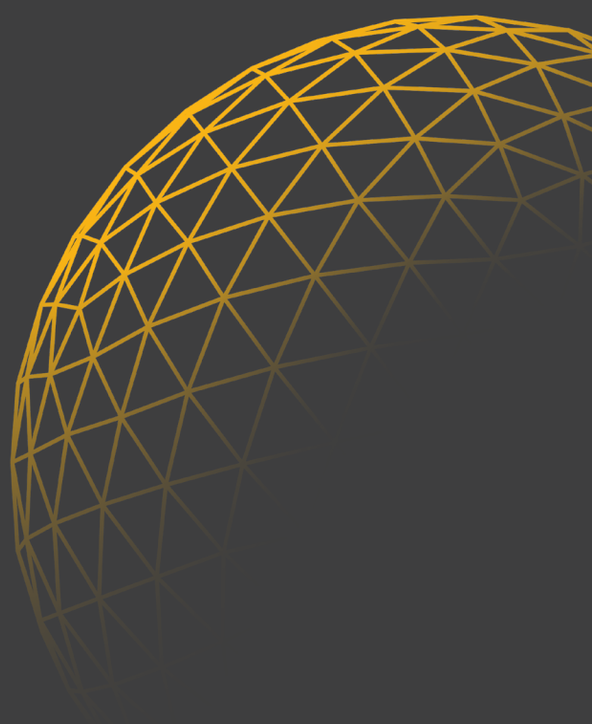
BREZTRI
AEROSPHERE®
(budesonide, glycopyrrolate, and formoterol fumarate)
Inhalation Aerosol

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

BREZTRI is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

For your symptomatic patients with COPD,

THE PROTECTION OF BREZTRI STARTS WITH YOU.



BREZTRI is administered as 2 inhalations, twice daily:
- Each inhalation delivers a combination of 160 mcg budesonide, 9 mcg glycopyrrolate, and 4.8 mcg formoterol fumarate

BREZTRI is the fastest-growing fixed-dose triple therapy with Pulmonologists for the treatment of COPD[1]*

*Growth does not imply comparable efficacy, safety, or FDA-approved indications. Based on new-to-brand volume and share growth during the period from [July 2020 to April 2022]. Actual number of prescriptions was [244,400]. Source: IQVIA NPA-MD.

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

IMPORTANT SAFETY INFORMATION (continued)

- 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 throughout and accompanying full Prescribing Information, including Patient Information.

AstraZeneca