Commissioned by AstraZeneca
Intended for UK healthcare professionals only

Guidelines

Trixeo® Aerosphere® (formoterol fumarate, glycopyrronium, and budesonide)

PRESCRIBING SUMMARY CARD

TRIXEO AEROSPHERE®
(formoterol fumarate, glycopyrronium, and budesonide) Inhalation Aerosol

Prescribing and adverse event reporting information is on pages 3–5.

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Trixeo® Aerosphere® (formoterol fumarate, glycopyrronium, and budesonide)

Guidelines

Indication[1]

- Trixeo Aerosphere® is indicated as a maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid (ICS) and a long-acting beta$_2$-agonist (LABA) or combination of a LABA and a long-acting muscarinic antagonist (LAMA).

Dose[1]

- The recommended and maximum dose is two inhalations twice daily (two inhalations in the morning, and two in the evening)
- If a dose is missed, it should be taken as soon as possible and the next dose should be taken at the usual time; a double dose should not be taken to make up for a forgotten dose.

Device[1]

- Trixeo Aerosphere is a pressurised metered dose inhaler (pMDI) that combines three agents in one device:
  - budesonide (ICS)
  - glycopyrronium (LAMA)
  - formoterol fumarate (LABA)

- Trixeo's innovative Aerosphere technology enables 38% to 41% deposition[2]
- The patient should be shown how to use the inhaler correctly by a healthcare professional and inhalation technique should be checked regularly
- Patients who find it difficult to coordinate actuation with inhalation may use Trixeo Aerosphere with a spacer to ensure proper administration of the medicinal product.

Guideline recommendations

Stepping up from dual to triple therapy[3]

- NICE recommends offering a LAMA+LABA+ICS for people with COPD who are taking LABA+ICS if:
  - their day-to-day symptoms continue to adversely impact their quality of life
  - or they have a severe exacerbation (requiring hospitalisation)
  - or they have two moderate exacerbations within a year
- NICE recommends considering a LAMA+LABA+ICS for people with COPD who are taking LAMA+LABA if:
  - they have a severe exacerbation (requiring hospitalisation)
  - or they have two moderate exacerbations within a year
- NICE recommends offering a 3-month trial of triple therapy for people with COPD who are taking LAMA+LABA and whose day-to-day symptoms adversely impact their quality of life. After 3 months, if symptoms have not improved, switch back to LAMA+LABA. If symptoms have improved, continue with LAMA+LABA+ICS.

Prescribing inhalers[3]

- NICE recommends minimising the number of inhalers and the number of different types of inhaler used by the patient, as far as possible[3]
- NICE recommends specifying the brand and inhaler in the prescription to ensure patients receive inhalers they have been trained to use.

Clinical evidence

- Patients with frequent exacerbations have a risk of death 4.3 times greater than patients with no exacerbations[4*]
- Trixeo Aerosphere protects against moderate and severe exacerbations[5]
- Trixeo Aerosphere reduces symptoms of COPD and improves quality of life vs formoterol/glycopyrronium MDI ($p<0.0001$) and formoterol/budesonide MDI** ($p<0.0001$).[6,7]

*In the 52-week ETHOS study (n=8588), Trixeo Aerosphere met the primary endpoint and significantly reduced the annual rate of on-treatment moderate/severe exacerbations by 24% (95% CI: 17, 31; p<0.0001) compared with FOR/GLY MDI (rate; 1.08 vs 1.42 events per patient year) and by 13% (95% CI: 5, 21; p=0.0027) compared with FOR/BUD MDI (rate; 1.08 vs 1.24 events per patient year).
**This regimen is not licensed in the UK.

Prescribing information: pages 3–5

Safety profile

- Trixeo Aerosphere's safety profile is consistent with the well-established profiles of its components[1,5,8]
- The most commonly reported adverse reactions in patients were pneumonia (4.6%), headache (2.7%), and urinary tract infection (2.7%).[1]

References

1. Trixeo Aerosphere 5 micrograms/7.2 micrograms/160 micrograms pressurised inhalation, suspension – summary of product characteristics. www.medicines.org.uk/emc/product/12028/smpc (Accessed July 2022)
2. van den Berge et al. Functional respiratory imaging assessment of budesonide/glycopyrrolate/formoterol fumarate and glycopyrrolate/formoterol fumarate metered dose inhalers in patients with COPD: the value of inhaled corticosteroids. *Respir Res* 2021; **22**: 191.
3. NICE. *Chronic obstructive pulmonary disease in over 16s: diagnosis and management.* Guideline 115. NICE, 2018. Last updated July 2019. www.nice.org.uk/ng115 (Accessed July 2022)
4. Soler-Cataluna JJ et al. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005; **60**: 925–931.
5. Rabe KF et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very severe COPD. *N Engl J Med* 2020; **383**: 35–48.
6. Martinez FJ et al. Benefits of budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler (BGF MDI) on symptoms and quality of life in patients with chronic obstructive pulmonary disease (COPD) in the ETHOS Trial. *Am J Respir Crit Care Med* 2020; **201**: A5073.
7. Rabe KF et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very severe COPD. *N Engl J Med* 2020; **383**: 35–48. (Supplementary Appendix).
8. Ferguson GT 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.

PRESCRIBING INFORMATION
TRIXEO AEROSPHERE® (formoterol fumarate/ glycopyrronium/ budesonide) 5 micrograms/7.2 micrograms/160 mg pressurised inhalation, suspension
Consult Summary of Product Characteristics before prescribing.
Indication: Trixeo Aerosphere is indicated as a maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist.
Presentation: Each single actuation (delivered dose, ex-actuator) contains 5mcg of formoterol fumarate dihydrate, glycopyrronium bromide 9mcg, equivalent to 7.2mcg of glycopyrronium and budesonide 160mcg. This corresponds to a metered dose of 5.8mcg of formoterol fumarate dihydrate, glycopyrronium bromide 10.4mcg, equivalent to 8.2mcg of glycopyrronium and budesonide 182mcg.
Dosage and Administration: The recommended and maximum dose is two inhalations twice daily (two inhalations morning and evening). If a dose is missed, take as soon as possible and take the next dose at the usual time. A double dose should not be taken to make up for a forgotten dose. **Special populations: Elderly:** No dose adjustments required in elderly patients. **Renal impairment:** Use at recommended dose in patients with mild to moderate renal impairment. Can also be used at the recommended dose in patients with severe renal impairment or end-stage renal disease requiring dialysis, only if expected benefit outweighs the potential risk. **Hepatic impairment:** Use at recommended dose in patients with mild to moderate hepatic impairment. Can also be used at the recommended dose in patients with severe hepatic impairment, only if expected benefit outweighs the potential risk. For inhalation use. To ensure proper administration of the medicinal product, the patient should be shown how to use the inhaler correctly by a physician or other healthcare professional, who should also regularly check the adequacy of the patient's inhalation technique. Patients who find it difficult to coordinate actuation with inhalation may use Trixeo Aerosphere with a spacer to ensure proper administration of the medicinal product.
Contraindications: Hypersensitivity to the active substances or to any of the excipients.
Warnings and Precautions: Not for acute use: Not indicated for treatment of acute episodes of bronchospasm, i.e. as a rescue therapy. **Paradoxical bronchospasm:** Administration of formoterol/glycopyrronium/budesonide may produce paradoxical bronchospasm with an immediate wheezing and shortness of breath after dosing and may be life-threatening. Treatment should be discontinued immediately if paradoxical bronchospasm occurs. Assess patient and alternative therapy instituted if necessary. **Deterioration of disease:** Recommended that treatment should not be stopped abruptly. If patients find the treatment ineffective, continue treatment but seek medical attention. Increasing use of reliever bronchodilators indicates worsening of the underlying condition and warrants reassessment of the therapy. Sudden and progressive deterioration in the symptoms of COPD is potentially life-threatening, patient should undergo urgent medical assessment. **Cardiovascular effects:** Cardiovascular effects, such as cardiac arrhythmias, e.g. atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists and sympathomimetics, including glycopyrronium and formoterol. Use with caution in patients with clinically significant uncontrolled and severe cardiovascular disease such as unstable ischemic heart disease, acute myocardial infarction, cardiomyopathy, cardiac arrhythmias and severe heart failure. Caution should also be exercised when treating patients with known or suspected prolongation of the QTc interval (QTc >

450 milliseconds for males or > 470 milliseconds for females), either congenital or induced by medicinal products. **Systemic corticosteroid effects:** May occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract and glaucoma. Potential effects on bone density should be considered particularly in patients on high doses for prolonged periods that have co-existing risk factors for osteoporosis. **Visual disturbances:** May be reported with systemic and topical corticosteroid use. If patient presents symptoms such as blurred vision or other visual disturbances, consider ophthalmologist referral for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR). **Transfer from oral therapy:** Care is needed in patients transferring from oral steroids, since they may remain at risk of impaired adrenal function for a considerable time. Patients who have required high dose corticosteroid therapy or prolonged treatment at the highest recommended dose of inhaled corticosteroids, may also be at risk. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery. **Pneumonia in patients with COPD:** An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. 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. Risk factors include current smoking, older age, low body mass index (BMI) and severe COPD. **Hypokalaemia:** Potentially serious hypokalaemia may result from β_2-agonist therapy. This has potential to produce adverse cardiovascular effects. Caution is advised in severe COPD as this effect may be potentiated by hypoxia. Hypokalaemia may also be potentiated by concomitant treatment with other medicinal products which can induce hypokalaemia, such as xanthine derivatives, steroids and diuretics. Hyperglycaemia: Inhalation of high doses of β_2-adrenergic agonists may produce increases in plasma glucose. Blood glucose should be monitored during treatment following established guidelines in patients with diabetes. **Co-existing conditions:** Use with caution in patients with thyrotoxicosis. **Anticholinergic activity:** Due to anticholinergic activity, use with caution in patients with symptomatic prostatic hyperplasia, urinary retention or with narrow-angle glaucoma. Patients should be informed about the signs and symptoms of acute narrow-angle glaucoma and should be informed to stop using this medicinal product and to contact their doctor immediately should any of these signs or symptoms develop. Co-administration of this medicinal product with other anticholinergic containing medicinal products is not recommended. **Renal impairment:** Patients with severe renal impairment (creatinine clearance of <30 mL/min), including those with end-stage renal disease requiring dialysis, should only be treated with this medicinal product if the expected benefit outweighs the potential risk. **Hepatic impairment:** In patients with severe hepatic impairment, use only if the expected benefit outweighs the potential risk. These patients should be monitored for potential adverse reactions.

Drug Interactions: Co-treatment with strong CYP3A inhibitors, e.g. itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products are expected to increase the risk of systemic side effects. Should be avoided unless the benefit outweighs the increased risk, in which case patients should be monitored for systemic corticosteroid adverse reactions. This is of limited clinical importance for short-term (1-2 weeks) treatment. **Other antimuscarinics and sympathomimetics:** Co-administration with other anticholinergic and/or long-acting β_2-adrenergic agonist containing medicinal products is not recommended as it may potentiate known inhaled muscarinic antagonist or β_2-adrenergic agonist adverse reactions. Concomitant use of other beta-adrenergic medicinal products can have potentially additive effects, caution required when prescribed concomitantly with formoterol. **Medicinal product-induced hypokalaemia:** Possible initial hypokalaemia may be potentiated by xanthine derivatives, steroids and non-potassium sparing diuretics. Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides. **β-adrenergic blockers:** β-adrenergic blockers (including eye drops) can weaken or inhibit the effect of formoterol. Concurrent use of β-adrenergic blockers should be avoided unless the expected benefit outweighs the potential risk. If required, cardio-selective β-adrenergic blockers are preferred. **Other pharmacodynamic interactions:** Concomitant treatment with quinidine, disopyramide, procainamide, antihistamines, monoamine oxidase inhibitors, tricyclic antidepressants and phenothiazines can prolong QT interval and increase the risk of ventricular arrhythmias. L-dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards beta2-sympathomimetics. Concomitant treatment with monoamine oxidase inhibitors, including medicinal products with similar properties such as furazolidone and procarbazine, may precipitate hypertensive reactions. Elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

Pregnancy and Lactation: Administration to pregnant women/women who are breast-feeding should only be considered if the expected benefit to the mother justifies the potential risk to the foetus/child.

Ability to Drive and Use Machines: Dizziness is an uncommon side effect which should be taken into account.

Undesirable events: Consult SmPC for full list of adverse events. **Common (≥ 1/100 to < 1/10):** Oral candidiasis, pneumonia, hyperglycaemia, anxiety, insomnia, headache, palpitations, dysphonia, cough, nausea, muscle spasms, urinary tract infection. **Uncommon (≥ 1/1,000 to < 1/100):** Hypersensitivity, depression, agitation, restlessness, nervousness, dizziness, tremor, angina pectoris, tachycardia, cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia and extrasystoles), bronchospasm, bruising, urinary retention, chest pain. **Very Rare (< 1/10,000):** Signs or symptoms of systemic glucocorticosteroid effects, e.g. hypofunction of the adrenal gland, abnormal behaviour. **Not known:** Angioedema, vision blurred, cataract, glaucoma.

Legal Category: POM.

Marketing Authorisation Number: EU/1/20/1498/002

Presentation & Basic NHS cost: 1 inhaler x 120 actuations:

Marketing Authorisation Holder: AstraZeneca AB, SE-151 85, Södertälje, Sweden.

Presentation & Basic NHS cost: 1 inhaler x 120 actuations: £44.50

Further Information is Available From: AstraZeneca UK Ltd, 600 Capability Green, Luton, LU1 3LU, UK.

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Date of preparation: 10/2020

RSP 20 0059

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to AstraZeneca by visiting https://aereporting.astrazeneca.com or by calling 0800 783 0033.

PRESCRIBING INFORMATION
BEVESPI AEROSPHERE
7.2 MICROGRAMS/5 MICROGRAMS PRESSURISED INHALATION, SUSPENSION (glycopyrronium/formoterol fumarate dihydrate)
Consult Summary of Product Characteristics before prescribing.
Indication: Bevespi Aerosphere is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Presentation: Pressurised inhalation, suspension. Each single actuation (delivered dose) contains glycopyrronium bromide 9 mcg equivalent to 7.2 mcg of glycopyrronium, and 5 mcg of formoterol fumarate dihydrate.
Dosage and Administration: Recommended dose is two inhalations twice daily. Patients should be advised not to take more than 2 inhalations twice daily. **Elderly:** No dose adjustment necessary. **Renal impairment:** No dose adjustment necessary in patients with mild to moderate renal impairment. Only use in patients with severe renal impairment or endstage disease requiring dialysis if benefits outweigh risks. **Hepatic impairment**: No dose adjustment necessary in patients with mild to moderate hepatic impairment. Use with caution in patients with severe hepatic impairment. **Paediatric population**: There is no relevant use (under 18 years) for the indication of COPD.
Contraindications: Hypersensitivity to the active substances or excipients.
Warnings and Precautions: Bevespi Aerosphere should not be used to treat Asthma. If paradoxical bronchospasm occurs, Bevespi Aerosphere should be discontinued immediately, and an alternative therapy instituted, if necessary. Bevespi is not indicated as rescue therapy for the treatment of acute episodes of bronchospasms. Cardiovascular effects, such as cardiac arrhythmias e.g. atrial fibrillation and tachycardia, may be seen after administration of muscarinic receptor antagonists and sympathomimetics, including glycopyrronium or formoterol. Use with caution in patients with severe cardiovascular disorders such asischaemic heart disease, tachyarrhythmias or severe heart failure. Exercise caution in patients with thyrotoxicosis or known/suspected prolongation of the QTc interval. β2-adrenergic agonists may produce significant hypokalaemia, which may increase the susceptibility to cardiac arrhythmias. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment. Inhalation of high doses of β2-adrenergic agonists may produce increases in plasma glucose. Use with caution in patients with symptomatic prostatic hyperplasia, urinary retention or with narrow-angle glaucoma. Bevespi Aerosphere should be used only if the expected benefit outweighs the potential risk for patients with severe renal impairment [(creatinine clearance of <30mL/min), including those with endstage renal disease requiring dialysis] and for patients with severe hepatic impairment. For severe hepatic impairment patients, monitor for potential adverse reactions.
Drug Interactions: Drug interactions may occur with medicinal products affecting renal excretion mechanisms. Concomitant use/co-administration with anticholinergic and/or longacting β2-adrenergic agonist containing medicinal products is not recommended as it may potentiate known inhaled muscarinic antagonist or β2-adrenergic agonist adverse reactions. Caution is advised with concomitant use with methylxanthine derivatives, steroids or nonpotassium-sparing diuretics may potentiate the possible initial hypokalaemic effect of β2-adrenergic agonists. Not to be given together with β2-adrenergic blockers (including eye drops) as can weaken or inhibit the effect of β-adrenergic agonists such as formoterol unless compelling reasons for their use. If β-adrenergic blockers are required (including eye drops), cardioselective β-adrenergic blockers are preferred, although they should also be administered with caution. Bevespi Aerosphere should be administered with caution to patients being treated with medicinal products known to prolong the QTc interval.
Pregnancy and Lactation: Administration to pregnant or breast-feeding women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus or child.
Ability to Drive and Use Machines: Dizziness and nausea are common side effects and patients who experience these symptoms should observe caution when driving or using machines.
Undesirable Events: Consult SmPC for full list of adverse events. **Common:** Anxiety, headache, dizziness, dry mouth, nausea, muscle spasms, urinary tract infection, chest pain. **Uncommon:** Hypersensitivity reactions including rash and pruritus, hyperglycaemia, agitation, restlessness, insomnia, tremor, tachycardia, palpitations, cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia and extrasystoles), urinary retention.
Legal Category: POM.
Marketing Authorisation Numbers: EU/1/18/1339/001
Presentation & Basic NHS Cost: 1 inhaler with 120 actuations: £32.50
Further Information is Available From: AstraZeneca UK Ltd., 600 Capability Green, Luton
LU1 3LU, UK.
Bevespi Aerosphere is a trade mark of the AstraZeneca group of companies.
Date of preparation: 01/2021
RSP 20 0057

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to AstraZeneca by visiting https://contactazmedical.astrazeneca.com or by calling 0800 783 0033.