New Medicine Assessment

Trixeo Aerosphere 5µg /7.2µg /160µg pressurised inhalation, suspension (5µg formoterol fumarate dihydrate, glycopyrronium bromide 9µg, equivalent to 7.2µg of glycopyrronium, and budesonide 160µg), 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 beta$_2$-agonist or combination of a long-acting beta$_2$-agonist and a long-acting muscarinic antagonist

Recommendation: GREEN (Restricted)

Restriction: Triple therapy should be reserved for patients who have failed to achieve or maintain an adequate response to an appropriate course of dual therapy.

This is in agreement with the LSCMMG RAG recommendations for the other inhaled triple therapies licensed for COPD.

Trixeo Aeropshere is licensed for patients with moderate to severe COPD who are not adequately treated by a combination of an ICS and LABA or combination of a LABA and a LAMA. The intended place in therapy for the Trixeo Aeropshere is in line with the 2019 NICE Guidelines for the treatment of patients with moderate to severe COPD for whom a MDI is considered clinically appropriate and who experience a severe exacerbation (requiring hospitalisation) or two moderate exacerbations within a year whilst receiving ICS/LABA or LAMA/LABA.[1]

This is also in line with the GOLD 2019 guidelines and the LSCMMG COPD desktop guideline.[2, 3]

Trixeo Aerosphere provides a device option that can be used with or without a spacer, for patients with COPD who prefer to use an MDI device and are unable to use, or unsuitable to receive other inhaler devices due to the nature of their lung function, breathing technique or dexterity concerns.

Summary of supporting evidence:

ETHOS: In a 52-week, phase 3, randomized trial to evaluate the efficacy and safety of triple therapy at two dose levels of inhaled glucocorticoid in patients with moderate-to-very-severe COPD and at least one exacerbation in the past year, patients were assigned in a 1:1:1:1 ratio to receive twice-daily inhaled doses of triple therapy (inhaled glucocorticoid [320 µg or 160 µg of budesonide], a LAMA [18 µg of glycopyrrolate], and a LABA [9.6 µg of formoterol]) or one of two dual therapies (18 µg of glycopyrrolate plus 9.6 µg of formoterol or 320 µg of budesonide plus 9.6 µg of formoterol). The primary end point was the annual rate (the estimated mean number per patient per year) of moderate or severe COPD exacerbations, as analyzed in the modified intention-to-treat population with the use of on-treatment data only.[4]

The modified intention-to-treat population comprised 8509 patients.

Triple therapy with twice-daily budesonide (at either the 160-µg or 320-µg dose), glycopyrrolate, and formoterol resulted in a lower rate of moderate or severe COPD exacerbations than glycopyrrolate–formoterol or budesonide–formoterol.

KRONOS: This was a double-blind, parallel-group, multicentre phase 3 randomised controlled trial.[5]

Eligible patients had an established clinical history of COPD, and were symptomatic for COPD, despite receiving two or more inhaled maintenance therapies for at least 6 weeks before screening. Patients were randomly assigned (2:2:1:1) to receive budesonide/glycopyrrolate/formoterol fumarate metered-dose inhaler 320/18/9·6 µg (BGF MDI),

glycopyrrolate/ formoterol fumarate metered-dose inhaler 18/9·6 µg (GFF MDI), budesonide/formoterol fumarate metered-dose inhaler 320/9·6 µg (BFF MDI), or open-label budesonide/formoterol fumarate dry-powder inhaler 400/12 µg (BUD/ FORM DPI).

Over 24 weeks, BGF MDI significantly improved FEV1 AUC0–4 versus BFF MDI (least squares mean difference 104 mL, 95% CI 77 to 131; p<0·0001) and BUD/FORM DPI (91 mL, 64 to 117; p<0·0001). BGF MDI also significantly improved pre-dose trough FEV1 versus GFF MDI (22 mL, 4 to 39; p=0·0139) and BFF MDI was non-inferior to BUD/FORM DPI (−10 mL, −36 to 16; p=0·4390). At week 24, patients in the BGF MDI group had a significantly improved FEV1 AUC0–4 compared with patients receiving BFF MDI (116 mL, 95% CI 80 to 152; p<0·0001); there was a non-significant improvement in the change from baseline in morning pre-dose trough FEV1 at week 24 versus GFF MDI (13 mL, −9 to 36 mL; p=0·2375).

Details of Review

Name of medicine (generic & brand name)**:**

Trixeo Aerosphere (formoterol fumarate dihydrate, glycopyrronium bromide and budesonide)

Strength(s) and form(s):

Pressurised inhalation, suspension, 5micrograms of formoterol fumarate dihydrate, glycopyrronium bromide 9 micrograms, equivalent to 7.2 micrograms of glycopyrronium, and budesonide 160 micrograms

Dose and administration:

The recommended and maximum dose is two inhalations twice daily (two inhalations in the morning and two inhalations 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.

BNF therapeutic class / mode of action

Trixeo Aerosphere contains contains budesonide, a glucocorticosteroid, and two bronchodilators: glycopyrronium, a long-acting muscarinic antagonist (anticholinergic) and formoterol, a long-acting β2-adrenergic agonist.

Budesonide is a glucocorticosteroid which when inhaled has a rapid (within hours) and dose dependent anti-inflammatory action in the airways.

Glycopyrronium is a long-acting, muscarinic antagonist, which is often referred to as an anticholinergic. The major targets for anticholinergic drugs are muscarinic receptors located in the respiratory tract. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation. Antagonism is competitive and reversible. Prevention of methylcholine and acetylcholine-induced bronchoconstrictive effects was dose-dependent and lasted more than 12 hours.

Formoterol is a selective β2-adrenergic agonist that when inhaled results in rapid and long-acting relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect is dose dependent, with an onset of effect within 1-3 minutes after inhalation. The duration of effect is at least 12 hours after a single dose.

Licensed indication(s):

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.[6]

Proposed use (if different from, or in addition to, licensed indication above):

Licensed indication

Course and cost:

Ongoing maintenance therapy.

£44.50 per inhaler (120 actuations = 30 days treatment)[7]

Current standard of care/comparator therapies: (NHS list price August 2021 DT)

Trelegy Ellipta: Fluticasone Furoate 92micrograms / dose + umeclidinium 55micrograms / dose + vilanterol 22micrograms / dose.

NHS list price = £44.50 / 30 days (based on 1 puffs / day)

Trimbow: Beclometasone 87micrograms / dose + formoterol 5micrograms / dose + glycopyrronium 9micrograms / dose

NHS list price = £44.50 / 30 days (based on 4 puffs / day)

Relevant NICE guidance:

Chronic obstructive pulmonary disease in over 16s: diagnosis and management

NICE guideline [NG115] Published: 05 December 2018 Last updated: 26 July 2019

Background and context

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 $beta_2$-agonist or combination of a long-acting $beta_2$-agonist and a long-acting muscarinic antagonist.

Trixeo Aerosphere offers an ICS / LABA /LAMA fixed dose combination in an MDI, as an alternative to Trimbow MDI or the dry powder triple inhaler Trelegy for the treatment of COPD.

The Trixeo Aerosphere may be useful in those patients for whom an MDI (with or without a spacer) is the most appropriate device.

This fits with the recommendations contained within the LSCMMG COPD Desktop Guideline.

Trixeo Aerosphere is delivered via Aerosphere co-suspension delivery technology that provides effective drug delivery of the dual fixed dose combination. The technology enables efficient combination, distribution and targeting of drugs to the lungs, with minimal shaking, consistent drug delivery when there is a delay from shake to actuation and consistent drug delivery from first to last dose.

Summary of evidence

Summary of efficacy data in proposed use:

The efficacy and safety of Trixeo Aerosphere was evaluated in patients with moderate to very severe COPD in two randomised, parallel-group trials, ETHOS and KRONOS. Both studies were multicentre, double-blind studies. Patients were symptomatic with a COPD Assessment Test (CAT) score ≥10 while receiving two or more daily maintenance therapies for at least 6 weeks prior to screening.

ETHOS was a 52-week trial (N=8,588 randomised; 60% male, mean age of 65) that compared two inhalations twice daily of Trixeo Aerosphere, formoterol fumarate dihydrate/glycopyrronium (FOR/GLY) MDI 5/7.2 µg, and formoterol fumarate dihydrate/budesonide (FOR/BUD) MDI 5/160 µg. Patients had moderate to very severe COPD (post-bronchodilator FEV1 ≥25% to <65% predicted) and were required to have a history of one or more moderate or severe COPD exacerbations in the year prior to screening. The proportion of patients with moderate, severe and very severe COPD was 29%, 61% and 11% respectively. The mean baseline FEV_1 across all groups was 1,021-1,066 mL, and during screening the mean post-bronchodilator percent predicted FEV1 was 43% and mean CAT score was 19.6. The primary endpoint of the ETHOS trial was the rate of on-treatment moderate or severe COPD exacerbations for Trixeo Aerosphere compared with FOR/GLY MDI and FOR/BUD MDI.

KRONOS was a 24-week trial (N=1,902 randomised; 71% male, mean age of 65) that compared two inhalations twice daily of Trixeo Aerosphere, FOR/GLY MDI 5/7.2 µg, FOR/BUD MDI 5/160 µg and open-label active comparator formoterol fumarate dihydrate/budesonide Turbuhaler (FOR/BUD TBH) 6/200 micrograms. Patients had moderate to very severe COPD (post-bronchodilator FEV1 ≥25% to <80% predicted). The proportion of patients with moderate, severe and very severe COPD was 49%, 43% and 8% respectively. The mean baseline FEV_1 across all groups was 1,050-1,193 mL, and during screening the mean post-bronchodilator percent predicted FEV_1 was 50%, over 26% of patients reported a history of one or more moderate or severe COPD exacerbation in the past year and the mean CAT score was 18.3. There was a 28-week extension, for up to 52 weeks of treatment, in a subset of subjects. The primary endpoints of the KRONOS trial were the on-treatment FEV_1 area under the curve from 0-4 hours (FEV1 AUC0-4) over 24 weeks for Trixeo Aerosphere compared to FOR/BUD MDI and the on-treatment change from baseline in morning pre-dose trough FEV_1 over 24 weeks for Trixeo Aerosphere compared to FOR/GLY MDI.

At study entry, the most common COPD medications reported in the ETHOS and KRONOS studies were ICS+LABA+LAMA (39%, 27% respectively), ICS+LABA (31%, 38% respectively) and LAMA+LABA (14%, 20% respectively).

Effect on exacerbations

Moderate or severe exacerbations:

In the 52-week ETHOS study, Trixeo Aerosphere 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).

The benefits observed on annualised rate of moderate/severe COPD exacerbations over 24 weeks in KRONOS were generally consistent with those observed in ETHOS. Improvements compared with FOR/GLY MDI were statistically significant; however improvements compared with FOR/BUD MDI and FOR/BUD TBH did not reach statistical significance.

Severe exacerbations (resulting in hospitalisation or death):

In ETHOS, Trixeo Aerosphere numerically reduced the annual rate of on-treatment severe exacerbations by 16% (95% CI: -3, 31; p=0.0944) compared with FOR/GLY MDI (rate; 0.13 vs 0.15 events per patient year) and significantly reduced the annual rate of on-treatment severe exacerbations by 20% (95% CI: 3, 34; p=0.0221) compared with FOR/BUD MDI (rate; 0.13 vs 0.16 events per patient year).

In both studies, benefits on exacerbations were observed in patients with moderate, severe and very severe COPD.

Effects on lung function

In ETHOS and KRONOS, Trixeo Aerosphere improved on-treatment lung function (FEV_1) compared with FOR/GLY MDI and FOR/BUD MDI (see Table 2 for ETHOS and Table 3 for KRONOS). There was a sustained effect over the 24-week treatment period in both studies, and over 52 weeks in ETHOS.

Lung function analyses – ETHOS (spirometric sub-study)

	Trixeo Aerosphere (N=747)	FOR/GLY MDI (N=779)	FOR/BUD MDI (N=755)	Treatment difference 95% CI	
				Trixeo Aerosphere vs. FOR/GLY MDI	Trixeo Aerosphere vs. FOR/BUD MDI
Trough FEV_1 (mL) over 24 weeks, LS mean change from baseline (SE)	129 (6.5)	86 (6.6)	53 (6.5)	43 mL (25, 60) p<0.0001	76 mL (58, 94) p<0.0001#
FEV_1 AUC_{0-4} over 24 weeks; LS mean change from baseline (SE)	294 (6.3)	245 (6.3)	194 (6.3)	49 mL (31, 66) p<0.0001#	99 mL (82, 117) p<0.0001

p-value not adjusted for multiplicity in hierarchical testing plan

LS = least squares, SE = standard error, CI = confidence intervals, N = number in Intent-to-Treat population

Lung function analyses – KRONOS

	Trixeo Aero-sphere (N=639)	FOR/ GLY MDI (N=625)	FOR/ BUD MDI (N=314)	FOR/ BUD TBH (N=318)	Treatment difference 95% CI		
					Trixeo Aerosphere vs. FOR/GLY MDI	Trixeo Aerosphere vs. FOR/BUD MDI	Trixeo Aerosphere vs. FOR/BUD TBH
Trough FEV_1 (mL) over 24 weeks, LS mean change from baseline (SE)	147 (6.5)	125 (6.6)	73 (9.2)	88 (9.1)	22 mL (4, 39) p=0.0139	74 mL (52, 95) p<0.0001	59 mL (38, 80) p<0.0001#
FEV_1 AUC_{0-4} over 24 weeks; LS mean change from baseline (SE)	305 (8.4)	288 (8.5)	201 (11.7)	214 (11.5)	16 mL (-6, 38) p=0.1448#	104 mL (77, 131) p<0.0001	91 mL (64, 117) p<0.0001

p-value not adjusted for multiplicity in hierarchical testing plan

LS = least squares, SE = standard error, CI = confidence intervals, N = number in Intent-to-Treat population

Symptom relief

In ETHOS, the baseline average dyspnoea scores ranged from 5.8 – 5.9 across the treatment groups. Trixeo Aerosphere significantly improved breathlessness (measured using the Transition Dyspnoea Index (TDI) focal score over 24 weeks) compared with FOR/GLY MDI (0.40 units; 95% CI: 0.24, 0.55; p<0.0001) and compared with FOR/BUD MDI (0.31 units; 95% CI: 0.15, 0.46; p<0.0001). Improvements were sustained over 52 weeks. In KRONOS, the baseline average dyspnoea scores ranged from 6.3 – 6.5 across the treatment groups. Trixeo Aerosphere significantly improved breathlessness over 24 weeks compared with FOR/BUD TBH (0.46 units; 95% CI: 0.16, 0.77; p=0.0031). Improvements compared with FOR/GLY MDI, and FOR/BUD MDI did not reach statistical significance.

Health-related quality of life

In ETHOS, Trixeo Aerosphere significantly improved disease-specific health status (as assessed by the St. George's Respiratory Questionnaire [SGRQ] total score) over 24 weeks compared with FOR/GLY MDI (improvement -1.62; 95% CI: -2.27, -0.97; p<0.0001) and compared with FOR/BUD MDI (improvement -1.38, 95% CI: -2.02, -0.73; p<0.0001). Improvements were sustained over 52

weeks. In KRONOS, improvements compared with FOR/GLY MDI, FOR/BUD MDI and FOR/BUD TBH did not reach statistical significance.

Use of rescue medication

In ETHOS, Trixeo Aerosphere significantly reduced the on-treatment use of rescue medication over 24 weeks compared with FOR/GLY MDI (treatment difference -0.51 puffs/day; 95% CI: -0.68, -0.34; p<0.0001) and FOR/BUD MDI (treatment difference -0.37 puffs/day; 95% CI: -0.54, -0.20; p<0.0001). Reductions were sustained over 52 weeks. In KRONOS, differences compared with FOR/GLY MDI, FOR/BUD MDI and FOR/BUD TBH were not statistically significant.

Summary of safety data

The safety profile is characterised by corticosteroid, anticholinergic and β_2-adrenergic class effects related to the individual components of the combination. The most commonly reported adverse reactions in patients receiving this medicinal product were pneumonia (4.6%), headache (2.7%) and urinary tract infection (2.7%).

Tabulated list of adverse reactions

The tabulated list of adverse reactions is based on the experience with this medicinal product in clinical trials and experience with the individual components.

Adverse reactions by frequency and system organ class (SOC)

System Organ Class	Preferred term	Frequency
Infections and infestations	Oral candidiasis Pneumonia	Common
Immune system disorders	Hypersensitivity	Uncommon
	Angioedema	Not known
Endocrine disorders	Signs or symptoms of systemic glucocorticosteroid effects, e.g. hypofunction of the adrenal gland	Very rare
Metabolism and nutrition disorders	Hyperglycaemia	Common
Psychiatric disorders	Anxiety Insomnia	Common
	Depression Agitation Restlessness Nervousness	Uncommon
	Abnormal behaviour	Very rare
Nervous system disorders	Headache	Common
	Dizziness Tremor	Uncommon
Eye disorders	Vision blurred (see section 4.4) Cataract Glaucoma	Not known
Cardiac disorders	Palpitations	Common
	Angina pectoris Tachycardia Cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia and extrasystoles)	Uncommon
Respiratory, thoracic and mediastinal disorders	Dysphonia Cough	Common
	Throat irritation Bronchospasm	Uncommon
Gastrointestinal disorders	Nausea	Common

	Dry mouth	Uncommon
Skin and subcutaneous tissue disorders	Bruising	Uncommon
Musculoskeletal and connective tissue disorders	Muscle spasms	Common
Renal and urinary disorders	Urinary tract infection	Common
	Urinary retention	Uncommon
General disorders and administration site conditions	Chest pain	Uncommon

The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from available data).

Strengths and limitations of the evidence:

Strengths: multicentre trials, large number of patients, length of studies, randomised / double blind

Limitations: Industry sponsored, no triple inhaler comparator

Summary of evidence on cost effectiveness:

The NHS list price of Trixeo Aerosphere is £44.50 per inhaler (120 actuations = 30 days treatment). Other available ICS/LAMA/LABA combination inhalers licensed for COPD are also £44.50 for 30 days treatment. Therefore, there is no cost implication.

Prescribing and risk management issues:

N/A

Innovation, need, equity:

The Trixeo Aerosphere provides an alternative MDI ICS/LAMA/LABA combination for the treatment of COPD, for those patients who are unable to use DPIs or for those for whom DPIs are clinically inappropriate.

The Aerosphere can be used with a spacer for those patients who have difficulty in co-ordinating actuation with inspiration of breath to ensure proper administration of the product.

References

[1] Chronic obstructive pulmonary disease in over 16s: diagnosis and management. NICE guideline [NG115]Published: 05 December 2018 Last updated: 26 July 2019 https://www.nice.org.uk/guidance/ng115

[2] Global Initiative For Chronic Obstructive Lung Disease 2019 report https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf

[3] LSCMMG COPD Desktop Guideline v1.8 https://www.lancsmmg.nhs.uk/media/1054/copd-guideline-version-18.pdf

[4] Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. Rabe K F et al. N Engl J Med 2020; 383:35-48 . https://www.nejm.org/doi/full/10.1056/NEJMoa1916046

[5] 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. Ferguson G T et al. The Lancet, Respiratory Medicine, VOLUME 6, ISSUE 10, P747-758, OCTOBER 01, 2018. https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(18)30327-8/fulltext

[6] SmPC Trixeo Aerosphere 5 micrograms/7.2 micrograms/160 micrograms pressurised inhalation, suspension. https://www.medicines.org.uk/emc/product/12028

[7] MIMS https://www.mims.co.uk/drugs/respiratory-system/asthma-copd/trixeo-aerosphere

Midlands and Lancashire Commissioning Support Unit,
Jubilee House, Lancashire Business Park, Leyland, PR26 6TR