MID AND SOUTH ESSEX MEDICINES OPTIMISATION COMMITTEE (MSEMOC)

FORMOTEROL FUMARATE DIHYDRATE / GLYCOPYRRONIUM / BUDESONIDE (TRIXEO® AEROSPHERE) TRIPLE THERAPY COMBINATION INHALER FOR THE TREATMENT OF COPD

GREEN - RECOMMENDED FOR RESTRICTED USE - for initiation in Primary, Community or Secondary care and continuation in Primary Care

Name: generic (trade)	What it is	Licensed indications	Decision status	NICE guidance
Formoterol fumarate dihydrate / glycopyrronium / budesonide (Trixeo®)	Fixed dose triple therapy combination of an inhaled corticosteroid (ICS- budesonide), a long-acting beta agonist (LABA- formoterol) and long-acting anti-muscarinic (LAMA- glycopyrronium)	Maintenance bronchodilator treatment to relieve symptoms in adult patients with Chronic obstructive Pulmonary disease (COPD)	Final	NICE- no guidance

MSEMOC recommendation:

Trixeo® is recommended for restricted use as a treatment option in line with local COPD treatment guidelines for stable category C or D patients where:

- all three components are clinically indicated
- A dry powder inhaler (DPI) is not an appropriate device
- Metered Dose Inhaler (MDI) is an appropriate device

Providers commissioned to provide services on behalf of Mid and South Essex CCGs are reminded that they are required to follow the local joint formulary and prescribing guidance, as detailed in the medicines management service specification of their contract.

Background information:

- Trixeo® is a fixed dose triple therapy combination inhaler (containing ICS- budesonide, LABA- formoterol & LAMA- glycopyrronium)
- It is licensed for use as maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD
- Trixeo® has been formulated to deliver 5 micrograms of formoterol fumarate dihydrate, 7.2 micrograms of glycopyrronium, and budesonide 160 micrograms
- **The recommended and maximum dose is two inhalations twice daily (two inhalations in the morning and two inhalations in the evening)**
- Each pressurised container has 120 actuations (30 day supply) and a shelf life of 24 months
- It is stored at room temperature prior to dispensing. After dispensing, the medicinal product may be stored for a maximum of 3 months at a temperature up to 30°C
- The annual cost of each inhaler is £541

ASSESSMENT AGAINST THE ETHICAL FRAMEWORK

Evidence of Clinical Effectiveness:

ETHOS:A 52-week, phase 3, randomized, double-blind, parallel-group study to asses triple inhaled therapy at two Glucocorticoid doses in moderate-to-very-severe COPD in 26 countries

- Objective: To assess 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 randomly assigned in a 1:1:1:1 ratio to receive triple therapy (an inhaled glucocorticoid at one of two dose levels [budesonide, 160 µg or 80 µg per inhaler actuation], a LAMA [glycopyrrolate, 9 µg per actuation], and a LABA [formoterol fumarate, 4.8 µg per actuation]) or one of two dual therapies (LAMA–LABA [glycopyrrolate, 9 µg per

actuation, and formoterol fumarate, 4.8 µg per actuation] or inhaled glucocorticoid–LABA [budesonide, 160 µg per actuation, and formoterol fumarate, 4.8 µg per actuation]). The patients received two doses per day over a 52-week period, and each dose consisted of two actuations (i.e., each dose of triple therapy delivered 320 µg or 160 µg of budesonide). Randomisation was stratified according to exacerbation history (1 or ≥2 moderate or severe exacerbations), postbronchodilator FEV1 (25 to <50% or 50 to <65% of the predicted normal value), blood eosinophil count (<150 or ≥150 cells per cubic millimetre), and country.

- Population: The modified intention-to-treat population comprised of 8509 patients aged 40 to 80 years old and had symptomatic COPD (defined as a score of ≥10 on the COPD Assessment Test, on which scores range from 0 to 40 with higher scores indicating more symptoms; the minimum clinically important difference is 2 points).
  All patients:
  - Were receiving at least two inhaled maintenance therapies at the time of screening, had a postbronchodilator ratio of a FEV1 to the forced vital capacity of less than 0.7, with a postbronchodilator FEV1 of 25 to 65% of the predicted normal value
  - Had a history of smoking of at least 10- packs of cigarettes a year
  - Had a documented history of at least one moderate to severe COPD exacerbation (if their FEV1 was <50% of the predicted normal value)
    Or
    at least two moderate or one severe COPD exacerbation (if FEV1 was ≥50% of the predicted normal value) in the year before screening

  Patients who had a current asthma diagnosis were excluded but those who had had asthma in the past were eligible.
- Intervention:
  - 2137 patients received 320-µg–budesonide triple-therapy
  - 2121 patients received 160-µg–budesonide triple-therapy
  - 2120 patients received glycopyrrolate–formoterol
  - 2131 patients received budesonide–formoterol
- Primary outcomes:
  Annual rate (the estimated mean number per patient per year) of moderate or severe COPD exacerbations); Trixeo® Aerosphere 1.08, glycopyrrolate-formoterol fumarate (GFF) 1.42
  budesonide-formoterol fumarate (BFF), 1.243.
  The annual rate of moderate or severe exacerbations was significantly lower with Trixeo® aerosphere versus comparators: Trixeo® aerosphere versus comparators, rate ratio (RR; 95% confidence interval [CI]); p value: GFF: 0.76 (0.69, 0.83); p<0.001. BFF: 0.87 (0.79, 0.95); p=0.0033
- Secondary outcomes:
  Time to first moderate/severe COPD exacerbation
  Patients with exacerbations, n (%): Trixeo® aerosphere: 1,026 (48.0),GFF: 1,056 (49.8),BFF: 1,085 (50.9).Trixeo® aerosphere showed a significant benefit over the dual-therapy regimens with respect to the time to first moderate/severe COPD exacerbation, hazard ratio (HR; 95% CI); p value: Trixeo® aerosphere versus: GFF: 0.88 (0.81, 0.96); p=0.004 BFF: 0.89 (0.81, 0.97); p=0.0063
  Annual rate of severe COPD exacerbations: Trixeo® aerosphere: 0.13, GFF: 0.15,BFF: 0.163
  Trixeo® aerosphere numerically (not statistically significant) reduced the annual rate of severe COPD exacerbations versus comparators, RR (95% CI); p value: Trixeo® aerosphere versus:
  GFF: 0.84 (0.69, 1.03); p=0.09, BFF: 0.80 (0.66–0.97); p=0.023

KRONOS: A randomized, double-blind, parallel-Group study to assess the efficacy and safety of triple therapy versus dual therapies in chronic obstructive pulmonary disease

- Objective: A phase 3 chronic-dosing, multi-center study to assess the efficacy and safety of triple therapy with budesonide/ glycopyrrolate/ formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease across 215 sites across 4 countries
- Population: The demographic characteristics of the patients at baseline were similar across treatment groups. Inclusion criteria: aged 40–80 years; current or former smokers (with a smoking history of ≥10 pack-years); established clinical history of COPD, as defined by the American Thoracic Society/European Respiratory Society or by locally applicable guidelines and confirmed by the investigator; and had moderate to very severe COPD, as defined by a postbronchodilator FEV1 less than 80% and 25% or more, according to predicted normal values using National Health and Nutrition Examination Survey III reference equations, or applicable reference norms for Japan and China (adjustment factor of 0.88). Patients were symptomatic (COPD Assessment Test score ≥10) despite receiving two or more inhaled maintenance therapies for at least 6 weeks before screening. Patients were not required to have had a COPD exacerbation within the preceding year.
- Intervention: 1902 patients were randomly assigned to received:
  - Trixeo® aerosphere (budesonide/glycopyrrolate/formoterol fumarate) MDI 320/14.4/9.6 µg (i.e. 160/7.2/4.8 µg as two inhalations twice-daily [licenced dose]; n=640)4
  - GFF MDI 18/9.6 µg (i.e. 9/4.8 µg as two inhalations twice-daily; n=627)
  - BFF MDI 320/9.6 µg (i.e. 160/4.8 µg as two inhalations twice-daily; n=316)

- Budesonide/formoterol fumarate dry powder inhaler 400/12 µg (BUD/FORM) DPI (i.e. 200/6 µg as two inhalations twice-daily; (n=319)

Participants received treatment as two inhalations twice-daily for 24 weeks.

- Primary outcomes:
  FEV1 area under the curve (AUC) 0−4, primary analysis
  Least squares mean (LSM) FEV1, mL (SE): Trixeo® aerosphere: 305 (8.4), GFF MDI: 288 (8.5), BFF MDI: 201 (11.7), BUD/FORM DPI: 214 (11.5)
  Over 24 weeks, Trixeo® aerosphere significantly improved FEV1 AUC0–4 versus BFF MDI and BUD/FORM DPI, LSM difference (95% confidence interval [CI]); p value: GFF MDI: 16 (–6, 38); p=0.1448,BFF MDI: 104 (77, 131); p<0.0001,BUD/FORM DPI: 91 (64, 117); p<0.0001
  Change from baseline in morning pre-dose trough FEV1, primary analysis.
  LSM, mL (SE): Trixeo® aerosphere: 147 (6.5), GFF MDI: 125 (6.6), BFF MDI: 73 (9.2), BUD/FORM DPI: 88 (9.1).
  The change from baseline in morning pre-dose trough FEV1 over 24 weeks was significantly improved by Trixeo® Aerosphere versus GFF MDI and BFF MDI, LSM difference (95% CI); p value: GFF MDI: 22 (4,39); p=0.0139, BFF MDI: 74 (52 to 95); p<0.0001, BUD/FORM DPI: 59 (38, 80); p<0.0001
- Secondary outcomes:
  FEV1 AUC0−4, secondary analysis LSM, mL (SE): Trixeo® aerosphere: 293 (8.4), GFF MDI: 271 (8.4), BFF MDI: 189 (11.6), BUD/FORM DPI: 204 (11.4).
  Over 24 weeks, Trixeo® Aerosphere significantly improved FEV1 AUC0–4 versus BFF MDI and BUD/FORM DPI, LSM difference (95% CI); p value: GFF MDI: 22 (0, 43); p=0.0488, BFF MDI: 104 (77, 130); p<0.0001, BUD/FORM DPI: 89 (63, 116); p<0.00014.
  Change from baseline in morning pre-dose trough FEV1, secondary analysis, LSM, mL (SE):
  Trixeo® Aerosphere: 137 (6.6), GFF MDI: 110 (6.6), BFF MDI: 63 (9.3), BUD/FORM DPI: 80 (9.2).
  The change from baseline in morning pre-dose trough FEV1 over 24 weeks was significantly improved by Trixeo® Aerosphere versus GFF MDI and BFF MDI, LSM difference (95% CI); p value: GFF MDI: 27 (9, 45); p=0.0027, BFF MDI: 74 (52, 96); p<0.0001, BUD/FORM DPI: 56 (35, 78); p<0.0001.
  Model-estimated rate of moderate or severe COPD exacerbations rate, per year: Trixeo® aerosphere: 0.46, GFF MDI: 0.95, BFF MDI: 0.56, BUD/FORM DPI: 0.554.The rate of moderate or severe COPD exacerbations was significantly lower during treatment with Trixeo® Aerosphere versus GFF MDI, rate ratio (95% CI); p value: GFF MDI: 0.48 (0.37, 0.64); p<0.0001, BFF MDI: 0.82 (0.58, 1.17); p=0.2792, BUD/FORM DPI: 0.83 (0.59, 1.18); p=0.3120.
  Change from baseline in use of rescue medication LSM, puffs per day (SE): Trixeo® aerosphere:1.3 (0.13),GFF MDI: –1.1 (0.13),BFF MDI: –1.1 (0.18),BUD/FORM DPI: –1.6 (0.17).
  There was no significant difference between Trixeo® Aerosphere and comparators in the use of daily rescue medication, LSM difference (95% CI); p value:GFF MDI: -0.25 (-0.60, 0.09); p=0.1446, BFF MDI: -0.24 (-0.65, 0.18); p=0.2661, BUD/FORM DPI: 0.23 (-0.17, 0.63); p=0.26674

Safety from Summary of Product Characteristics (SPC):

The safety profile is characterised by corticosteroid, anticholinergic and β2-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%).

Limitations and comments:

- The studies were initiated & sponsored by AstraZeneca
- Long term safety data was limited due to the short durations of the trials
- Triple therapy versus dual therapy was assessed.

Cost of treatment and Cost Effectiveness:

- No cost-effectiveness analysis available.
- The annual cost of trixeo® is similar to that of other LABA/LAMA/ICS combination products, at the same point in the MSE COPD pathway
- 1st line (licensed) LAMA + LABA + ICS choices administered together as separate inhalers: £541/year vs £577-£962/year
- Where triple therapy is indicated and effective there is a potential for reduced costs by using fixed dose triple therapy (LAMA, LABA & ICS) in a single inhaler versus 2 separate inhalers (e.g. LAMA /LABA + ICS)

Inhaler	Type	Dose	Cost/ year	equivalent miles in a car/year)ø
Fluticasone/vilanterol/umeclidinium 92/22/55mcg (Trelegy Ellipta®)	DPI	One puff daily	£541	34
Beclometasone/formoterol/glycopyrronium 88/5/9mcg (Trimbow Nexthaler®)	DPI	Two puffs twice daily	£541	39
Budesonide/formoterol/glycopyrronium 160/5/7.2 (Trixeo Aerosphere®)	MDI	Two puffs twice daily	£541	593
Beclometasone/formoterol/glycopyrronium 87/5/9mcg (Trimbow MDI®) #	MDI	Two puffs twice daily	£541	624

The needs of the population:

- The needs of the population appear to be low as there are a range of single (LAMA, LABA, ICS) and dual therapy (LAMA/LABA) combination inhalers available to treat COPD.
- Where triple therapy is indicated, twice daily administration with one inhaler vs two may be an attractive option for patient adherence (including difficulty using more than 1 device or who find their medication regimen difficult or confusing) even though the clinical relevance has not been established
- Fixed triple therapy lacks flexibility and makes it difficult to amend the individual medicines if treatment needs changing for any reason
- There are concerns that the availability of a fixed dose triple therapy inhaler may lead to rapid escalation to triple therapy with no assessment of the need, efficacy and safety of the separate individual drugs (especially the ICS – given safety concerns)

The needs of the community:

- The needs of the community can be considered as low as Trixeo® is similar cost as alternative LAMA/LABA/ICS combination inhalers.
- There may be potential cost savings to the wider system if there is a response to treatment, treatment costs associated with poorly controlled disease may be avoided (e.g. a reduction in treatments needed for exacerbations, including hospitalisation) at the expense of the ongoing drug cost.
- Costs would be increased if there is rapid escalation to triple therapy and subsequent reduced use of lower cost LABA/LAMA inhalers

Equity and Equality:

- No impact anticipated.

Policy drivers:

- **NICE guidelines for COPD in over 16s: diagnosis and management** NG115
- **Global Initiative for Chronic Obstructive Lung Disease (GOLD)** Report 2021.
- **NHS Long term Plan**, link
- **NHSE Network Contract Directed Enhanced Service: Investment and Impact Fund**, link
- **Trixeo® aerosphere**

  Scottish Medicines Consortium:
  Issued the following advice following an abbreviated submission:
  Formoterol fumarate dihydrate / glycopyrronium / budesonide (Trixeo® aerosphere) is accepted for restricted use within NHS Scotland (in patients with severe COPD (forced expiratory volume in one second [FEV1] less than 50% predicted normal) for 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

  All Wales medicines strategy group (AWSMSG):
  Trixeo® aerosphere was excluded from appraisal by AWSMSG as it meets exclusion criteria 6 (below). Overall it is not endorsed by the body 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.
  Criteria 6: Product is a new formulation or combination of an established medicine which is either:
  - an oral formulation intended for patients unable to swallow tablets or capsules, or;
  - an alternative formulation of an established medicine which costs the same or less than the existing established medicine*.

  *New formulations costing more will be considered on case-by-case basis

  EoE CCG decisions:
  - **Bedfordshire Luton and Milton Keynes ICS (accessed February 2022)**
    Issued a green (i.e. appropriate for initiation in both primary and secondary care)

  Other decisions:
  - **NHS Derbyshire CCGs (accessed February 2022):**
    Issued a grey (i.e. for use except in exceptional circumstances only) traffic light status
  - **Greater Manchester Medicines Management Group (accessed February 2022):**
    Accepted for use as a single triple therapy combination inhaler
  - **Lancashire & South Cumbria (accessed February 2022):**
    Issued a grey traffic light status (i.e. prioritised for review)

Implementability:

- Requires engagement from primary, community and secondary care to ensure equity across the local health economies.

References:

- NICE guidelines for COPD in over 16s: diagnosis and management https://www.nice.org.uk/guidance/ng115
- GOLD report 2021 https://goldcopd.org/2021-gold-reports/
- NHS Long term Plan, January 2019(https://www.longtermplan.nhs.uk/)
- NHSE. Network Contract Directed Enhanced Service Investment and Impact Fund 2021/22: Updated Guidance 01 December 2021(https://www.england.nhs.uk/publication/investment-and-impact-fund-2021-22-implementation-guidance/)

- Scottish Medicines Consortium- Trixeo® (advice Feb 2021) https://www.scottishmedicines.org.uk/media/5765/formoterol-fumarate-dihydrate-Trixeo®-aerosphere-abb-final-jan-2021-for-website.pdf
- All Wales medicines strategy group- Trixeo® (advice Nov 2020) https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-appraisals/formoterol-glycopyrronium-bromide-budesonide-Trixeo®-aerosphere/
- British Thoracic Society, Position Statement – the Environment and Lung Health 2020 https://www.brit-thoracic.org.uk/document-library/governance-and-policy-documents/position-statements/environment-and-lung-health-position-statement-2020/
- Primary Care Respiratory Society – Evaluation of appropriateness of inhaled corticosteroid (ICS) therapy in COPD and guidance on ICS withdrawal https://www.pcrs-uk.org/sites/pcrs-uk.org/files/SteppingDownICS_FINAL5.pdf
- Right Breathe https://www.rightbreathe.com/
- PrescQIPP Lowering the inhaler carbon footprint data tool: https://www.prescqipp.info/news/lowering-the-inhaler-carbon-footprint-data-tool/
- Drug Tariff online (Jan 2022): https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff
- Electronic medicines consortium, AstraZeneca UK Limited. Trixeo® Aerosphere 5 micrograms/7.2 micrograms/160 micrograms pressurised inhalation, suspension [accessed 21st Jan 2022]. https://www.medicines.org.uk/emc/product/12028
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- Ferguson GT, Rabe KF, Martinez FJ, Fabbri LM, Wang C, Ichinose M, 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. The Lancet Respiratory medicine. 2018;6(10):747-58. Available from https://pubmed.ncbi.nlm.nih.gov/30232048/ [accessed 21st Jan 2022].

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