Mid and South Essex Health and Care Partnership

NHS

MID AND SOUTH ESSEX MEDICINES OPTIMISATION COMMITTEE (MSEMOC)

GLYCOPYRRONIUM/FORMOTEROL (BEVESPI® AEROSPHERE) DUAL 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
Glycopyrronium/ formoterol (Bevespi®)	Fixed dose dual therapy combination of an inhaled 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:

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

- dual components are clinically indicated
- the Spiolto Respimat SMI (soft mist inhaler) is not an appropriate device due to dexterity issues
- 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:

- Bevespi® is a fixed dose dual therapy combination of an inhaled a long-acting beta-agonist (LABA- formoterol) and long-acting anti-muscarinic (LAMA- glycopyrronium)
- It is licensed for use as maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD
- Bevespi® has been formulated to deliver 7.2 micrograms of glycopyrronium, and 5 micrograms of formoterol fumarate dihydrate
- **The recommended 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 30 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 £395

ASSESSMENT AGAINST THE ETHICAL FRAMEWORK

Evidence of Clinical Effectiveness:

PINNACLE 1: Efficacy and safety of glycopyrrolate/formoterol metered dose inhaler formulated using co-suspension delivery technology in patients with COPD

- Objective: To assess the efficacy and safety of bevespi® Aerosphere, formoterol fumarate MDI, glycopyrronium MDI, and open label tiotropium bromide inhalation powder compared with each other and placebo MDI over 24 weeks in subjects with moderate to very severe COPD.
- Population: Adult subjects aged ≥40–≤80 years with an established clinical history of COPD as defined by the 2004 American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria. Subjects were current or former smokers with a history of ≥10 pack years of cigarette smoking, post-bronchodilator FEV1/FVC ratio <0.70, and FEV1 <80% predicted normal value. The study involved 160 sites in Australia, New Zealand and the USA.

- Intervention: A phase 3 placebo-controlled, double-blind, multi-centre, randomised controlled trial(RCT) where patients were randomised in a 7:6:6:6:3 ratio to receive either (N=2,103):
    - Bevespi® Aerosphere (n=527)
    - Glycopyrronium MDI (n=451)
    - Formoterol fumarate MDI (n=452)
    - Tiotropium (n=453)
    - Placebo (n=220)
- Primary outcome:
  Change from baseline in morning pre-dose trough FEV1 at Week 24.
  At week 24, differences in change from baseline in the morning pre-dose trough FEV1 for bevespi® Aerosphere compared with placebo MDI, glycopyrronium MDI, formoterol fumarate MDI, and tiotropium were 150 mL, 59 mL, 64 mL (all p<0.0001), and 21 mL (p<0.01), respectively.
- Secondary outcome:
  Change from baseline in morning pre-dose trough FEV1 over 24 weeks:
  The change from baseline in morning pre-dose trough FEV1 over 24 weeks was similar to that observed for the primary outcome; differences in change from baseline for bevespi® Aerosphere compared with placebo MDI, glycopyrronium MDI, formoterol fumarate MDI, and tiotropium were 158 mL, 60 mL, 64 mL (all p<0.0001), and 29 mL (p<0.01), respectively.
  Change from baseline in average daily rescue albuterol use over 24 weeks:
  There was a significant reduction in rescue albuterol use over 24 weeks in patients taking bevespi® Aerosphere compared with placebo MDI and tiotropium:
  At week 24, differences in change from baseline for Bevespi® Aerosphere compared with placebo MDI, glycopyrronium MDI, formoterol fumarate MDI, and tiotropium were –1.08 puffs/d (p<0.0001), –0.26 puffs/d, –0.01 puffs/d, and –0.34 puffs/d (p<0.05), respectively.

PINNACLE-2: Efficacy and safety of glycopyrrolate/formoterol metered dose inhaler formulated using co-suspension delivery technology in patients with COPD.

- Objective: To assess the efficacy and safety of Bevespi® Aerosphere, glycopyrronium MDI, and formoterol fumarate MDI in subjects with moderate to very severe COPD.
- Population: Adult subjects aged ≥40–≤80 years with an established clinical history of COPD as defined by the 2004 ATS/ERS criteria.32 Subjects were current or former smokers with a history of ≥10 pack years of cigarette smoking, postbronchodilator FEV1/FVC ratio <0.70, and FEV1 <80% predicted normal value. Study took place across 140 sites in the USA.
- Intervention: A phase 3, placebo-controlled, double-blind, multi-centre, RCT where patients were randomised in a 7:6:6:3 ratio to receive either (N=1,615):
    - Bevespi® Aerosphere (n=512)
    - Glycopyrronium MDI (n=440)
    - Formoterol fumarate MDI (n=439)
    - Placebo (n=224)
- Primary outcome:
  Change from baseline in morning pre-dose trough FEV1 at Week 24
  At week 24, differences in change from baseline in the morning pre-dose trough FEV1 for Bevespi® Aerosphere compared with placebo MDI, glycopyrronium MDI, and formoterol fumarate MDI were 103 mL (p<0.0001), 54 mL (p<0.001), and 56 mL (p<0.001), respectively.
- Secondary outcome:
  Change from baseline in morning pre-dose trough FEV1 over 24 weeks
  The change from baseline in morning pre-dose trough FEV1 over 24 weeks was similar to that observed for the primary outcome: Differences in change from baseline for Bevespi® Aerosphere compared with placebo MDI, glycopyrronium MDI, and formoterol fumarate MDI were 129 mL, 55 mL, and 57 mL (all p<0.0001), respectively.
  Change from baseline in average daily rescue albuterol use over 24 weeks
  There was a significant reduction in rescue albuterol use over 24 weeks in patients taking Bevespi® Aerosphere compared with placebo MDI, glycopyrronium MDI, and formoterol fumarate MDI: At week 24, differences in change from baseline for Bevespi® Aerosphere compared with placebo MDI, glycopyrronium MDI, formoterol fumarate, and tiotropium were –1.04 puffs/d (p<0.0001), –0.57 puffs/d (p<0.0001), and –0.29 puffs/d (p<0.05), respectively.

PINNACLE 3: Long-term safety and efficacy of glycopyrrolate/formoterol metered dose inhaler using novel Co-Suspension™ Delivery Technology in patients with chronic obstructive pulmonary disease

- Objective: To assess the long-term safety and tolerability of bevespi® Aerosphere, glycopyrronium MDI, and formoterol fumarate MDI in subjects with moderate to very severe COPD (over 52 weeks).
- Population: Adult subjects who completed either PINNACLE-1 or PINNACLE-2, aged ≥40–≤80 years with an established clinical history of COPD as defined by the 2004 ATS/ERS criteria. Subjects were current or former smokers with a history of ≥10 pack years of cigarette smoking, postbronchodilator FEV1/FVC ratio <0.70, and FEV1 <80% predicted normal value. The study was undertaken in 205 sites in Autralia, New Zealand and the USA.
- Interventions: A phase 3, double-blind, multi-centre, parallel-group, active-controlled, RCT extension study where patients were randomised to receive either (N=892):

- Bevespi® Aerosphere (n=290)
- Glycopyrronium MDI (n=218)
- Formoterol fumarate MDI (n=213)
- Tiotropium (n=171)

- Primary outcome:
  Change from baseline in morning pre-dose trough FEV1 over 52 weeks
  At week 52, differences in change from baseline in the morning pre-dose trough FEV1 for bevespi® Aerosphere compared with glycopyrronium MDI, formoterol fumarate MDI, and tiotropium were 57 mL, 65 mL (all p<0.0001), and 25 mL (p<0.0117), respectively.
- Secondary outcome:
  Peak change from baseline in FEV1 within 2 hours post-dose at Week 52 bevespi® Aerosphere showed significant improvements compared with glycopyrronium MDI, formoterol fumarate MDI, and tiotropium: At week 52, differences in change from baseline for Bevespi® Aerosphere compared with glycopyrronium MDI, formoterol fumarate MDI, and tiotropium were 129 mL, 88 mL, and 93 mL (all p<0.0001), respectively.

PINNACLE 4: Improved lung function and patient-reported outcomes with co-suspension delivery technology glycopyrrolate/formoterol fumarate metered dose inhaler in COPD: a randomized Phase III study conducted in Asia, Europe, and the USA.

- Objective: To assess the efficacy and safety of Bevespi® Aerosphere, glycopyrronium MDI, and formoterol fumarate MDI in subjects with moderate to very severe COPD
- Population: As per the inclusion criteria reported for PINNACLE-1 and PINNACLE-2: aged ≥40–≤80 years with an established clinical history of COPD as defined by the 2004 ATS/ERS criteria. Subjects were current or former smokers with a history of ≥10 pack years of cigarette smoking, postbronchodilator FEV1/FVC ratio <0.70, and FEV1 <80% predicted normal value. The study was performed in 167 sites in Asia, Europe and USA.
- Intervention: Patients were randomised to receive either (N=1,756):
  - Bevespi® Aerosphere (n=555)
  - Glycopyrronium MDI (n=480)
  - Formoterol fumarate MDI (n=483)
  - Placebo (n=238)
- Primary outcome:
  Change from baseline in morning pre-dose trough FEV1 at Week 24
  At week 24, differences in change from baseline in the morning pre-dose trough FEV1 for bevespi® Aerosphere compared with placebo MDI, glycopyrronium MDI, and formoterol fumarate MDI were 165 mL, 59 mL, and 72 mL (all p<0.0001), respectively.
- Secondary outcome:
  Change from baseline in morning pre-dose trough FEV1 over 24 weeks.
  The change from baseline in morning pre-dose trough FEV1 over 24 weeks was similar to that observed for the primary outcome: Differences in change from baseline for Bevespi® Aerosphere compared with placebo MDI, glycopyrronium MDI, and formoterol fumarate MDI were 155 mL, 55 mL, and 72 mL (all p<0.0001), respectively.
  Peak change from baseline in FEV1 within 2 hours post-dose at Week 24
  Bevespi® Aerosphere showed significant improvements compared with placebo, glycopyrronium MDI, and formoterol fumarate MDI: At week 24, differences in change from baseline for Bevespi® Aerosphere compared with placebo MDI, glycopyrronium MDI, and formoterol fumarate MDI were 303 mL, 145 mL, and 111 mL (all p<0.0001), respectively.
  Change from baseline in mean daily rescue albuterol use over 24 weeks
  There was a significant reduction in rescue albuterol use over 24 weeks in patients taking Bevespi® Aerosphere compared with placebo MDI, glycopyrronium MDI, and formoterol fumarate MDI:At week 24, differences in change from baseline for Bevespi® Aerosphere compared with placebo MDI, glycopyrronium MDI, and formoterol fumarate were –0.98 puffs/d (p<0.0001), –0.77 puffs/d (p<0.0001), and –0.41 puffs/d (p=0.0345), respectively.

Vs Umeclidinium/Vilanterol Dry Powder Inhaler: A Randomized, Double-Blind, Double-Dummy Study of Glycopyrrolate/Formoterol Fumarate Metered Dose Inhaler (GFF MDI) relative to Umeclidinium/Vilanterol Dry Powder Inhaler (UV DPI) in COPD.

- Objective: To assess the efficacy and safety of Glycopyrrolate/Formoterol Fumarate Metered Dose Inhaler (GFF MDI) relative to umeclidinium/vilanterol dry powder inhaler (UV DPI) in patients with moderate-to-very severe chronic obstructive pulmonary disease (COPD).
- Population: Eligible patients were male or female, 40–95 years of age, with a current clinical diagnosis of COPD (forced expiratory volume in 1s [FEV1]/forced vital capacity [FVC] ratio < 0.70), an FEV1 < 80% of predicted normal value, and a smoking history of at least 10 pack-years. The study was performed at 110 centers in Bulgaria, Canada, France, Hungary, Russia, Ukraine, and the USA.
- Intervention: Patients (n= 1119) were randomized in a 1:1 scheme to the GFF MDI 18/9.6 ug (equivalent to glycopyrronium/formoterol fumarate dehydrate 14.4/10 ug) and UV DPI 62.5/25 ug treatment groups.
- Primary outcomes:
  Change from baseline in morning pre-dose trough forced expiratory volume in 1 s (FEV1) and peak change from baseline in FEV1 within 2 h post-dose, both over 24 weeks.

GFF MDI was non-inferior to UV DPI (using a margin of - 50 mL) for peak FEV1 (least squares mean [LSM] difference - 3.4 mL, 97.5% confidence interval [CI] - 32.8, 25.9) but not for trough FEV1 (LSM difference - 87.2 mL; - 117.0,- 57.4). However, treatment with GFF MDI was shown to have a more rapid onset of action. Exacerbation and safety findings were similar between groups. GFF MDI was non-inferior to UV DPI in the PP (per protocol) analysis set for peak change from baseline in FEV1 within 2 h post-dosing (treatment difference - 3.4 mL; 97.5% CI - 32.8, 25.9).

- Secondary outcomes:
  Secondary lung function endpoints were the onset of action on day 1 (proportion of patients with an increase in FEV1 of at least 100 mL from baseline at 5 min post-dosing) and the peak change from baseline in inspiratory capacity (IC) within 2 h post-dosing.
  For peak change from baseline in IC within 2 h post-dosing, non-inferiority for GFF MDI vs UV DPI was not shown in the PP analysis set (- 15.2 mL; 95% CI - 53.4, 22.9), but the lower bound of the 95% CI was within the non-inferiority margin in the full analysis set (treatment difference - 12.7 mL; 95% CI - 49.8, 24.3).
  Secondary symptom endpoints were Transition Dyspnoea Index (TDI) focal score and change from baseline in Early Morning Symptoms COPD Instrument (EMSCI) score. Other symptom endpoints included change from baseline in Night-Time Symptoms COPD Instrument (NiSCI) score and CAT score. Time to first moderate or severe COPD exacerbation was an exploratory endpoint. All secondary and other endpoints were assessed over 24 weeks except onset of action on day 1. Overall, no clinically meaningful differences were observed between the two treatments in symptom endpoints.
  GFF MDI was nominally superior to UV DPI for onset of action ($p < 0.0001$) and was nominally non-inferior to UV DPI for all symptom endpoints (Transition Dyspnea Index focal score, Early Morning/Night-Time Symptoms COPD instrument scores, and COPD Assessment Test score).
  Similar numbers of patients in each treatment group had at least one moderate or severe COPD exacerbation during the treatment period: 107 events in 92 patients (16.7%) in the GFF MDI group and 111 events in 97 patients (17.6%) in the UV DPI group. There were no meaningful differences between treatment groups in the time to first moderate or severe COPD exacerbation (hazard ratio 0.97; 95% CI 0.73, 1.29)

Safety from Summary of Product Characteristics (SPC):

The safety profile is characterised by anticholinergic and β2-adrenergic class effects related to the individual components of the combination. The most common adverse reactions reported in the clinical development program (comprised of 1,588 patients receiving bevespi® Aerosphere) were headache (1.9%), nausea (1.4%), muscle spasms (1.4%), and dizziness (1.3%).

Limitations and comments:

- The studies were initiated & sponsored by AstraZeneca
- Long term safety data was limited due to the short durations of the trials

Cost of treatment and Cost Effectiveness:

- No cost-effectiveness analysis available.
- The monthly and annual cost of bevespi® is similar to that of other LAMA + LABA combination products, at the same point in the MSE COPD pathway
- 1st line (licensed) LAMA + LABA choices administered together vs separate inhalers: £395/year vs £378-£835/year
- Where dual therapy is indicated and effective there is a potential for reduced costs by using fixed dose dual therapy (LAMA/LABA) in a single inhaler versus 2 separate inhalers (e.g. LAMA + LABA)

Inhaler	Type	Dose	Cost/ year	equivalent miles in a car/year)ʊ
Umeclidinium/vilanterol 55/22mcg (Anoro Ellipta®)	DPI	One puff daily	£395	32
Aclidinium/formoterol 400/12mcg (Duaklir Genuair®)	DPI	One puff twice daily	£395	24
Glycopyrronium/indacaterol 85/43mcg (Ultibro ® Breezhaler®)	DPI	One puff daily	£395	25
Tiotropium/olodaterol 2.5/2.5mcg (Spiolto ® Respimat®)	SMI	Two puffs daily	£395	0.03
Glycopyrronium/formoterol 7.2/5mcg (Bevespi® Aerosphere®)	MDI	Two puffs twice daily	£395	576

The needs of the population:

- The needs of the population appear to be low as there are a range dual therapy (LAMA/LABA) combination inhalers available to treat COPD.
- Fixed dual 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 dual therapy inhaler may lead to rapid escalation to dual therapy with no assessment of the need, efficacy and safety of the separate individual drugs

The needs of the community:

- The needs of the community can be considered as low as Bevespi® is similar cost as alternative LAMA/LABA 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.

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

Scottish Medicines Consortium:
Issued the following advice in the absence of a submission from the manufacturer:
glycopyrronium / formoterol fumarate dihydrate (bevespi® aerosphere®) is not recommended for use within NHS Scotland for maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease

All Wales medicines strategy group (AWSMSG):
Bevespi® aerosphere was excluded from appraisal by AWSMSG as it meets exclusion criteria 6 (below). Overall it is not endorsed by the body for maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease .
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 green (i.e. suitable for use initiation in primary care) second line LABA/LAMA traffic light status
- **Greater Manchester Medicines Management Group (accessed February 2022):**
  Accepted for use as a single LAMA/LABA inhaler combination
- **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:

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- Scottish Medicines Consortium- Bevespi® (advice May 2021) https://www.scottishmedicines.org.uk/medicines-advice/glycopyrroniumformoterol-fumarate-dihydrate-bevespi®-aerosphere-non-sub-smc2377/
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- 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/
- 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/
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