New Medicine Assessment

Bevespi Aerosphere 7.2 µg/5 micrograms pressurised inhalation, suspension (glycopyrronium bromide 9 µg equivalent to 7.2 µg of glycopyrronium, and 5 µg of formoterol fumarate dihydrate) as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Recommendation: GREEN

Bevespi Aerosphere provides the only LAMA/LABA dual fixed combination MDI licensed for the treatment of COPD.

The intended place in therapy for the Bevespi Aeropshere is in line with the 2019 NICE Guidelines for patients receiving their first maintenance treatment ie a fixed dose combination of LAMA/LABA and in patients who require a step-up in therapy when limited by symptoms or have exacerbations despite prior treatment.[1]

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

Bevespi 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:

PINNACLE 1,2[4] **and 4**[5]

The clinical development program for Bevespi Aerosphere included three 24-week, randomised, double-blind, placebo-controlled, parallel-group pivotal Phase III studies in 5,433 patients with moderate to very severe COPD

In three Phase III, 24-week studies (PINNACLE 1, PINNACLE 2 and PINNACLE 4) Bevespi Aerosphere provided improvements over placebo in lung function (as measured by morning pre-dose trough forced expiratory volume in 1 second [FEV_1]), with a demonstrated onset of action at 5 minutes following administration of the first dose on Day 1 (improvement over placebo by 187mL, 186 mL and 179 mL in PINNACLE 1, PINNACLE 2 and PINNACLE 4, respectively [p <0.001]) and also patient reported outcomes.

PINNACLE 3[6] was a long term safety and efficacy study and was open to adult patients who completed either PINNACLE 1 or PINNACLE 2. This was a Phase 3, double blind, multicentre, parallel group, active controlled RCT extension study. 892 patients were included, study length was 52 weeks.

Details of Review

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

Bevespi Aerosphere (glycopyrronium bromide and formoterol fumarate dihydrate)

Strength(s) and form(s):

Pressurised inhalation, suspension, 7.2 micrograms/5 micrograms pressurised inhalation, suspension (glycopyrronium bromide 9 micrograms equivalent to 7.2 micrograms of glycopyrronium, and 5 micrograms of formoterol fumarate dihydrate)

Dose and administration:

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

Patients should be advised not to take more than 2 inhalations twice daily.

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

Bevespi Aerosphere contains two bronchodilators: glycopyrronium a long-acting muscarinic antagonist (LAMA, also referred to as an anticholinergic) and formoterol a long-acting β_2-adrenergic agonist (LABA) with a rapid onset of action.

Licensed indication(s): [7]

Bevespi Aerosphere is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)

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

Licensed indication

Course and cost:

Ongoing maintenance therapy.

£32.50 per inhaler (120 actuations = 30 days treatment)[8]

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

Duaklir 340micrograms / dose / 12micrograms / dose Genuair (Aclidinium bromide 396micrograms/dose + Formoterol 11.8micrograms/dose)

NHS list price = £32.50 / 30 days (based on 2 puffs / day)

Ultibro Breezhaler 85microgram / 43microgram inhalation powder capsules with device (Indacaterol 85micrograms/dose + Glycopyrronium bromide 54micrograms/dose)

NHS list price = £32.50 / 30 days (based on 1 puffs / day)

Spiolto Respimat 2.5micrograms / dose / 2.5micrograms / dose solution for inhalation cartridge with device (Tiotropium bromide 2.5micrograms/dose + Olodaterol 2.5micrograms/dose)

NHS list price = £32.50 / 30 days (based on 2 puffs / day)

Anoro Ellipta 55micrograms / dose / 22micrograms / dose dry powder inhaler (Umeclidinium bromide 65micrograms/dose + Vilanterol 22micrograms/dose)

NHS list price = £32.50 / 30 days (based on 1 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

Bevespi Aerosphere is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease.

Bevespi Aerosphere offers a LABA /LAMA fixed dose combination in an MDI, as opposed to other LABA/LAMA combinations licensed for use in COPD which are either delivered by soft mist inhalers or dry powder inhalers. The Bevespi 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.

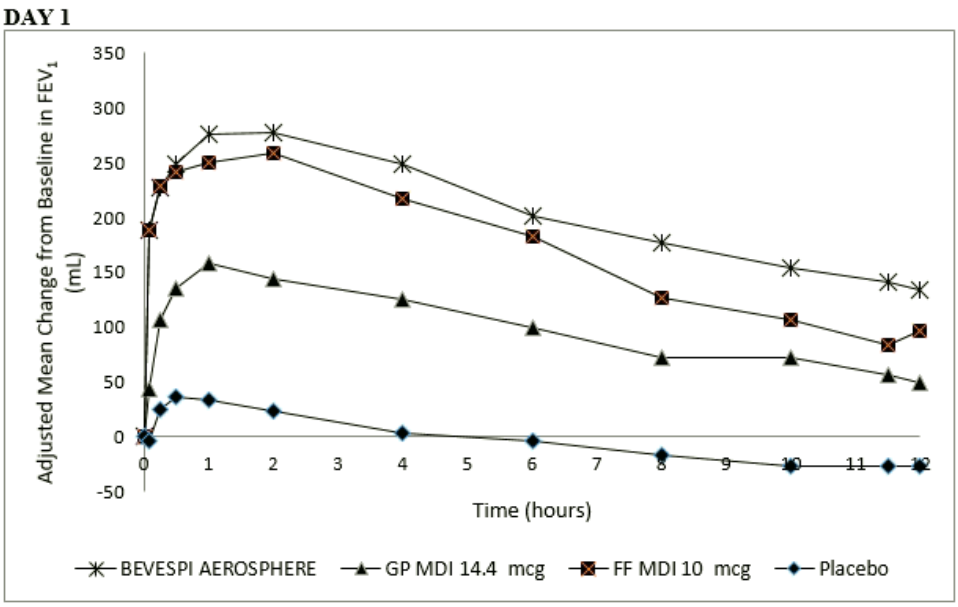
Bevespi Aerosphere is delivered via Aerosphere co-suspension delivery technology that provides effective drug delivery of the dual fixed dose combination. The technology enables efficient combination, distribution and targeting of drugs to the lungs, with minimal shaking, consistent drug delivery when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

Summary of evidence

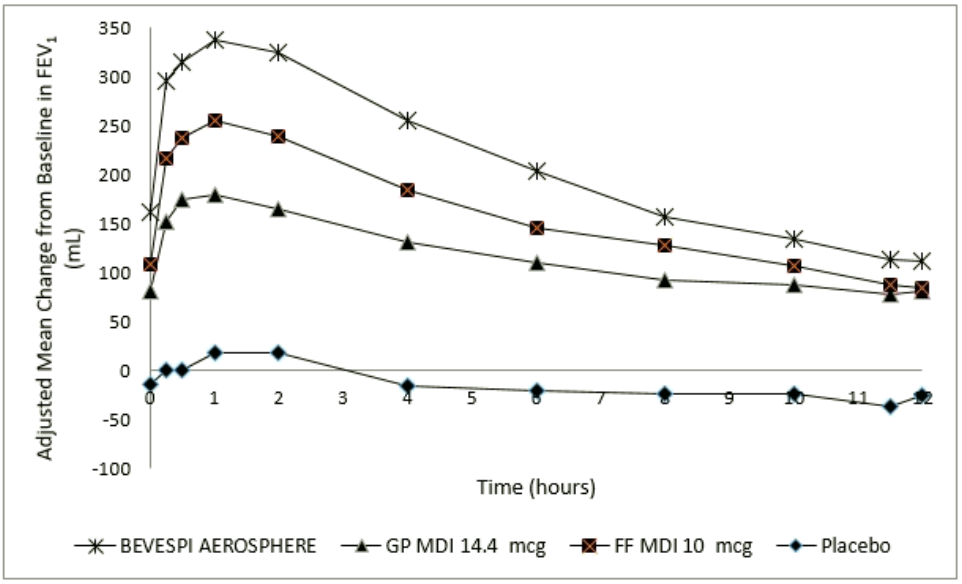
Summary of efficacy data in proposed use:

In three Phase III, 24-week studies (PINNACLE 1, PINNACLE 2 and PINNACLE 4) Bevespi Aerosphere provided improvements over placebo in lung function (as measured by morning pre-dose trough forced expiratory volume in 1 second [FEV_1]), with a demonstrated onset of action at 5 minutes following administration of the first dose on Day 1 (improvement over placebo by 187 mL, 186 mL and 179 mL in PINNACLE 1, PINNACLE 2 and PINNACLE 4, respectively [p <0.001]). The mean bronchodilator effect derived from serial FEV_1 measurements at Day 1 and Week 12 from PINNACLE 1 are shown in Figure 1. In PINNACLE 2, the results were similar to those observed in PINNACLE 1.

Figure 1 - Mean Change from Baseline in FEV_1 over Time on Day 1 and at Week 12



WEEK 12



Clinical efficacy

The clinical development program for Bevespi Aerosphere included three 24-week, randomised, double-blind, placebo-controlled, parallel-group pivotal Phase III studies in 5,433 patients with moderate to very severe COPD (PINNACLE 1, PINNACLE 2 and PINNACLE 4).

Effects on lung function

In studies PINNACLE 1, PINNACLE 2 and PINNACLE 4, Bevespi Aerosphere showed improvements in trough FEV_1 over 24 weeks relative to placebo, glycopyrronium and formoterol ($p<0.0001$) [see Table 2]. There was no attenuation of the bronchodilator effect over time. Bevespi Aerosphere also showed improvements in peak FEV_1 within 2 hours post-dose over 24 weeks relative to placebo, glycopyrronium and formoterol ($p<0.0001$) [see Table 2].

There were improvements in trough FEV_1 irrespective of age, sex, degree of airflow limitation, baseline symptoms, smoking status, or inhaled corticosteroid use.

Symptomatic outcomes

Breathlessness:

In PINNACLE 1 and PINNACLE 2, Bevespi Aerosphere provided improvements in breathlessness as demonstrated by Self-administered Computerised Transitional Dyspnoea Index (SAC TDI) focal score over 24 weeks compared to placebo and glycopyrronium (see Table 2). Improvements compared to formoterol were observed in PINNACLE 2 (see Table 2). In PINNACLE 4, Bevespi Aerosphere provided improvements in breathlessness as demonstrated by TDI focal score over 24 weeks compared to placebo and glycopyrronium (see Table 2).

Health-related quality of life:

In PINNACLE 1, PINNACLE 2 and PINNACLE 4, Bevespi Aerosphere provided an improvement in disease-specific health-related quality of life, as indicated by a reduction in the St George's Respiratory Questionnaire (SGRQ) total score over 24 weeks compared to placebo and glycopyrronium [see Table 2]. There were improvements compared to formoterol in PINNACLE 1 and PINNACLE 2.

Table 2 Lung function, symptomatic and health related quality of life outcomes over 24 weeks

Treatment comparisons with Bevespi Aersophere	Treatment difference (95% confidence intervals, p-value)				
	Trough FEV_1 (ml)[a]	Peak FEV_1 (ml)	SAC-TDI / TDI Focal Score[b]	SGRQ total score	Daily rescue Ventolin (inhalations/ day)[c]
PINNACLE 1					
Bevespi Aerosphere (N=526) vs placebo (N=219)	158 (132, 183) p<0.0001	288 (259, 317) p<0.0001[#]	0.47 (0.21, 0.72) p=0.0003	-2.39 (-4.07, -0.71) p=0.0053[#]	-1.08 (-1.43, -0.73) p<0.0001[#]
Bevespi Aerosphere (N=526) vs Glycopyrronium (N=451)	60 (39, 80) p<0.0001	123 (100, 146) p<0.0001[#]	0.27 (0.07, 0.47) p=0.0086[#]	-1.90 (-3.24, 0.57) p=0.0052[#]	-0.26 (-0.53, 0.01) p=0.0619
Bevespi Aerosphere (N=526) vs formoterol fumarate (N=449)	64 (44, 84) p<0.0001	81 (59, 104) p<0.0001[#]	0.16 (-0.03, 0.36) p=0.1060	-0.75 (-2.08, 0.57) p=0.2640	-0.01 (-0.27, 0.26) p=0.9683
PINNACLE 2					
Bevespi Aerosphere (N=510) vs placebo (N=223)	129 (103, 155) p<0.0001	278 (249, 308) p<0.0001	0.33 (0.11, 0.56) p=0.0041	-1.66 (-3.34, 0.02) p=0.0534	-1.04 (-1.37, -0.72) p<0.0001
Bevespi Aerosphere (N=510) vs Glycopyrronium (N=439)	55 (34, 76) p<0.0001	129 (106, 153) p<0.0001	0.21 (0.03, 0.40) p=0.0199	-1.28 (-2.62, 0.06) p=0.0605	-0.57 (-0.83, -0.31) p<0.0001
Bevespi Aerosphere (N=510) vs formoterol fumarate (N=437)	57 (36, 78) p<0.0001	76 (52, 99) p<0.0001	0.28 (0.10, 0.46) p=0.0028	-1.22 (-2.56, 0.13) p=0.0760	-0.29 (-0.55, -0.03) p=0.0274[#]
PINNACLE 4					
Bevespi Aerosphere (N=551) vs placebo (N=235)	155 (129, 180) p<0.0001	293 (265, 321) p<0.0001	0.80 (0.47, 1.13) p<0.0001	-3.50 (-5.18, -1.82) p<0.0001	-0.98 (-1.47, -0.49) p<0.0001
Bevespi Aerosphere (N=551) vs glycopyrronium (N=474)	55 (35, 76) p<0.0001	141 (119, 163) p<0.0001	0.33 (0.07, 0.59) p=0.0125	-1.62 (-2.94, -0.30) p=0.0165	-0.77 (-1.16, -0.38) p<0.0001
Bevespi Aerosphere (N=551) vs formoterol fumarate (N=480)	72 (52, 92) p<0.0001	97 (75, 119) p<0.0001	0.15 (-0.11, 0.41) p=0.2530	-0.27 (-1.59, 1.05) p=0.6908	-0.41 (-0.80, -0.03) p=0.0345[#]

[N] number in Intent to Treat population
[a] primary endpoint in all studies

[b] PINNACLE 1 and PINNACLE 2 used SAC-TDI. PINNACLE 4 used TDI. SAC-TDI was a primary endpoint in PINNACLE 1 and PINNACLE 2 only
[c] From the Rescue Ventolin User Population in PINNACLE 4
[#] A hierarchical statistical testing procedure was used in this study and this comparison was below a comparison that did not achieve statistical significance. Therefore, statistical significance on this comparison cannot be inferred.
COPD exacerbations:

The individual studies were not specifically designed to evaluate the effect of treatments on COPD exacerbations and patients were withdrawn from the studies if a severe exacerbation or more than 2 moderate exacerbations.

Other efficacy data:

PINNACLE 3 was a long term safety and efficacy study and was open to adult patients who completed either PINNACLE 1 or PINNACLE 2. This was a Phase 3, double blind, multicentre, parallel group, active controlled RCT extension study. 892 patients were randomised to either:

Bevspi Aerospher n = 290

Glycopyrronium MDI n= 218

Formoterol fumarate MDI n=213

Tiotropium n= 171

Primary Endpoint Results = Change from baseline in morning pre dose trough FEV_1 over 52 weeks. At week 52, differences in changes from baseline in morning pre dose trough FEV1 for Bevespi aerosphere compared to glycopyrronium MDI, formoterol MDI and tiotropium were 57ml, 65ml (all p<0.0001) and 25ml (p<0.0117) respectively.

Secondary endpoints = peak change from baseline in FEV_1 within 2 hours post dose at week 52. Bevespi Aerosphere showed significant improvements compared to glycopyrronium MDI, formoterol MDI and tiotropium – 129ml, 88ml and 93ml (all p<0.0001) respectively.

Summary of safety data

The safety profile is characterised by anticholinergic and β_2-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%).

Tabulated list of adverse reactions

The tabulated list of adverse reactions is based on the experience with Bevespi Aerosphere in clinical trials and experience with the individual components and related products.

Adverse reactions by frequency and system organ class (SOC)

System Organ Class	Preferred term	Frequency
Immune system disorders	Hypersensitivity reactions including rash and pruritus	Uncommon
Metabolism and nutrition disorders	Hyperglycaemia[1]	Uncommon
Psychiatric disorders	Anxiety	Common
	Agitation Restlessness Insomnia	Uncommon
Nervous system disorders	Headache[1] Dizziness	Common
	Tremor[1]	Uncommon

Cardiac disorders	Tachycardia Palpitations Cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia, and extrasystoles)	Uncommon
Gastrointestinal disorders	Dry mouth[2], Nausea	Common
Musculoskeletal and connective tissue disorders	Muscle spasms[1]	Common
Renal and urinary disorders	Urinary tract infection	Common
	Urinary retention[2]	Uncommon
General disorders and administration site conditions	Chest pain	Common

[1] adverse reaction relates to formoterol
[2] adverse reaction relates to glycopyrronium

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

Limitations: Industry sponsored, limited dual therapy comparator data (comparators only given as separate inhalers)

Summary of evidence on cost effectiveness:

The NHS list price of Bevespi Aerosphere is £32.50 per inhaler (120 actuations = 30 days treatment). Other available LAMA/LABA combination inhalers licensed for COPD are also £32.50 for 30 days treatment. Therefore, there is no cost implication as it would be used as an alternative.

Prescribing and risk management issues:

N/A

Innovation, need, equity:

The Bevespi Aerosphere provides the only MDI 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] PINNACLE 1 and 2 - Efficacy and Safety of Glycopyrrolate/Formoterol Metered Dose Inhaler Formulated Using Co-Suspension Delivery Technology in Patients With COPD. Martinez F J et al. Chest. 2017 Feb;151(2):340-357. https://pubmed.ncbi.nlm.nih.gov/27916620/

[5] 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. Lipworth BJ et al. Int J Chron Obstruct Pulmon Dis. 2018 Sep 26;13:2969-2984. https://pubmed.ncbi.nlm.nih.gov/30310273/

[6] 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. Hanania N A et al. Respir Med. 2017 May;126:105-115. https://pubmed.ncbi.nlm.nih.gov/28427541/

[7] Bevespi Aerosphere 7.2 micrograms/5 micrograms pressurised inhalation, suspension SmPC https://www.medicines.org.uk/emc/product/12024

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

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