MTRAC
Midlands Therapeutics Review and Advisory Committee

Commissioning Support
Fixed-dose LABA/LAMA inhalers:
Ultibro Breezhaler▼, Anoro Ellipta ▼, Duaklir Genuair▼, Spiolto Respimat

For the treatment of chronic obstructive pulmonary disease (COPD)

Commissioning guidance points for consideration:

- It was the opinion of the Committee, based on specialist advice, that the choice between LABA/LAMA inhalers was highly dependent on the patients' ability to tolerate and use the inhaler device.
- Before stepping up treatment, the patients' inhaler technique, compliance with administration instructions, and tolerance of the current device should be checked. In patients who struggle to learn new inhaler technique or to adjust to new devices, local practitioners advise that when stepping up inhaler treatment is indicated, use of a fixed-dose combination using the same device type as the former treatment may be helpful.
- In the 2010 NICE guideline on the management of COPD, LABA in addition to a LAMA are recommended in people who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, have FEV_1 less than 50% of predicted during spirometric testing and have declined or cannot tolerate an inhaled corticosteroid. LABA plus aLAMA is also a treatment option in people with persistent exacerbations or breathlessness despite maintenance therapy with a LABA in people who have declined or cannot tolerate an inhaled corticosteroid. (n.b. LABA/LAMA combination inhalers were not available at the time this guidance was developed, and were not considered by NICE.).
- The 2017 GOLD report's advice on the treatment of stable COPD recommends stepping up to a combination long-acting beta agonist/long-acting muscarinic antagonist (LABA/LAMA) inhaler as first-choice fixed-dose combination therapy, when initial treatment with a single long-acting bronchodilator is insufficient for patients graded as B, C or D (high risk of exacerbations or high symptom impact scores). De-escalation of treatment where the introduction of additional inhaled therapy has not improved symptoms is also recommended. See GOLD 2017 for the full advice.
- COPD guidance from the Pan-Birmingham Respiratory Network also recommends LABA/LAMA therapy when stepping-up from therapy with a single long-acting inhaler (a LAMA [preferred] or LABA if contraindicated).
- Factors to consider should CCGs wish to rationalise the number of products available on the formulary include patient acceptability and cost, the use of licensed products at licensed doses, and the available local and national guidance.

Description of the technology

This overview describes fixed-dose LABA/LAMA combination inhaled treatments containing two long-acting bronchodilator components with different mechanisms of action and receptor targets within the lungs. Four LABA/LAMA fixed-dose combination inhalers are currently licensed for the treatment of COPD in the UK (Ultibro Breezhaler[1], Anoro Ellipta[2], Duaklir Genuair[3] and Spiolto Respimat[4]). See Table 1 overleaf for details.

Evidence for efficacy and safety

A 2016 network meta-analysis[5] investigated the comparative efficacy of different LABA/LAMA FDC inhalers in COPD. The analysis included 27 trials (n = 30,361) and analysed data for: lung function (trough FEV_1), breathlessness (Transition Dyspnoea index; TDI), exacerbation rates (all exacerbations; moderate + severe exacerbations; severe exacerbations) and health-related quality of life (St George's Respiratory Questionnaire; SGRQ). The analysis reported only one significant difference, and that was for trough FEV_1 for Anoro Ellipta *vs*. Duaklir Genuair after adjustments for baseline severity and concomitant use of ICS. There were no significant differences between the different LABA/LAMA inhalers for any other outcomes.

A systematic review of FDC combination inhalers for COPD[6] included data from five trials evaluating Ultibro Breezhaler or Anoro Ellipta *vs.* Seretide Accuhaler. The meta-analyses found statistically significant (but only slightly greater) improvements in lung function with LABA/LAMA *vs.* Seretide Accuhaler but there was considerable heterogeneity between the trials. Exacerbations were less frequently observed in the LABA/LAMA treatment arm than LABA/ICS (odds ratio 0.77 [95% CI: 0.62 to 0.96]). This result was driven by trials evaluating Ultibro Breezehaler *vs*. Seretide Accuhaler.

The trials included below and summarised in the box are the fully published, phase 3 RCTs that have evaluated a LABA/LAMA FDC inhaler and have reported patient-oriented primary outcomes (exacerbations, breathlessness, health status [SGRQ]). Where no such patient-oriented outcome data are available for an inhaler, disease-oriented outcomes (e.g. lung function data) have been provided. The summary box includes the direct head-to-head comparative trial evidence evaluating fixed-dose combination inhalers *versus* another fixed-dose combination, available at the time of consideration of the evidence. Not all LABA/LABA combination inhalers have been compared in RCTs.

Effectiveness:[a]

Mortality was not reported as a primary outcome measure in any LABA/LAMA trials.

Exacerbations:

- The FLAME trial[7] reported lower exacerbation rates (all exacerbations, and moderate to severe exacerbations requiring hospitalisation) with Ultibro Breezhaler *vs*. Seretide Accuhaler over 52 weeks.
- The AFFIRM trial evaluated exacerbations (any requiring intervention: dose adjustment, antibiotic treatment, or hospitalisation) as a secondary outcome and found no significant difference for Duaklir Genuair *vs*. Seretide Accuhaler over 24 weeks.[8]

Breathlessness:

no significant difference was reported in Transition Dyspnoea index scores for Anoro Ellipta *vs*. Seretide Accuhaler 500/50 in a 12-week RCT.[9]

Safety:

- *Pneumonia:* In the FLAME trial[7], the incidence of radiologically-confirmed pneumonia was lower in the Ultibro Breezhaler group (3.2%) than in the Seretide Accuhaler group (4.8%) (p = 0.02; NNH ~ 60 over one year's treatment with Seretide Accuhaler compared with Ultibro Breezhaler).
- *Cardiovascular risk:* patients with clinically significant uncontrolled cardiovascular diseases were generally excluded from trials of these products, and there is therefore no experience of use in these patient groups.

Across the trials, the most commonly reported adverse events were worsening of COPD, nasopharyngitis and cough.

Cost: yearly cost, excluding VAT; Source MIMs Online, August 2016):

Anoro Ellipta	£395
Ultibro Breezhaler	£395
Duaklir Genuair	£395
Spiolto Respimat	£395

Patient factors:

- Patient acceptability of a particular inhalation device and adherence to treatment is a major factor affecting the success of inhaled treatments. The likelihood of finding an acceptable treatment may be enhanced by choices relating to frequency of administration and formulation (see Table 1 for details of individual products).
- Quality of life improvement scores using the St George's Respiratory Questionnaire (SGRQ) were primary outcomes for RCTs involving Anoro (1 trial[10]) and Spiolto (4 trials[11,12]). Both products showed significantly and clinically important (≥4 point improvement) improvements *vs*. placebo from baseline, and significantly more participants showed a response to treatment (≥4 point improvement). Spiolto also showed statistically significantly greater improvement that its individual components, tiotropium and olodaterol[11].

Ultibro Breezhaler

In the 52-week FLAME trial[7] (n = 3,362), participants with COPD (post-bronchodilator FEV_1 25% to 60% predicted) and a prior history of exacerbations in the previous year were randomised to treatment with Ultibro Breezhaler or Seretide Accuhaler (salmeterol 50 µg / fluticasone propionate 500 µg). There was a significantly lower annual rate of all exacerbations (primary outcome), and moderate to severe exacerbations requiring hospitalisation with Ultibro Breezhaler than with Seretide Accuhaler.

The SPARK[13] trial (n = 2,224) enrolled adults with severe COPD (FEV_1 < 50% predicted[13]), and at least one prior exacerbation of COPD[13]. This study reported a 12% reduction in the primary outcome (annualised rate of moderate or severe exacerbations) for Ultibro Breezhaler compared with monotherapy with the LAMA glycopyrronium. The rate of all exacerbations was also significantly lower with Ultibro Breezhaler compared with glycopyrronium (p < 0.0012) and with open-label tiotropium (p < 0.0017).[13]

The BLAZE trial[14] (n = 247; 6-week crossover study) found significantly greater improvements in the primary outcome of dyspnoea with Ultibro Breezhaler *vs.* placebo and tiotropium. Participants enrolled in this trial had severe COPD (post-bronchodilator FEV_1 of 30% to 80%[14]).

Five further trials[15-18] reported significantly greater improvements in lung function (trough FEV_1 or FEV_1 AUC_{0-12}) for adults using the Ultibro Breezhaler compared with Seretide Accuhaler 500/50 over 26 weeks' treatment in two trials[15,17]; and indacaterol, glycopyrronium, open-label tiotropium or placebo in the remaining trials.[16,18]

Anoro Ellipta

A 12-week trial[9] compared Anoro Ellipta with Seretide Accuhaler 500/50 for the treatment of adults with COPD, and reported significantly greater improvements in lung function (0-24 h weighted mean FEV_1 and trough FEV_1) for Anoro Ellipta. There was no significant difference for symptom-related or quality of life outcomes (TDI, SGRQ).[19] A second RCT[20] found that Anoro Ellipta was non-inferior to tiotropium + indacaterol as separate inhalers for measures of lung function (0-6 h WM FEV_1), breathlessness and SGRQ over 12 weeks.

In four, 24-week trials of adults with COPD and post-bronchodilator FEV_1 < 70% predicted (total n = 4,149)[21-23], Anoro Ellipta treatment showed significantly greater

Table 1: Details of fixed-dose LABA/LAMA combination inhalers available in the UK

Constituents and doses[ab] licensed for COPD **Brand name and Summary of Product Characteristics (SPC)**	**Licensed indication**	**Dose[a]** DPI: dry powder inhaler SMI: soft mist inhaler
Indacaterol/ glycopyrronium (110 µg/54 µg) Ultibro Breezhaler▼[1]	Maintenance broncho-dilator treatment to relieve symptoms in adult patients with COPD	DPI: One inhalation, once daily
Vilanterol/ umeclidinium (22 µg/55 µg) Anoro Ellipta▼[2]		DPI: One inhalation, once daily
Formoterol/ aclidinium bromide (11.8 µg/340 µg) Duaklir Genuair ▼[3]		DPI: One inhalation, twice daily
Tiotropium bromide/olodaterol (2.5µg/2.5µg) Spiolto Respimat[4]		SMI: Two inhalations, once daily

[a] *Doses shown are 'delivered doses (actual dose leaving mouthpiece) as per SPC description.* [b] *The doses shown do not represent the full range that can be used, and they do not imply therapeutic equivalence.*

improvement in the primary outcome of lung function (trough FEV_1) than tiotropium or its individual components (vilanterol and umeclidinium). Time to first exacerbation was a secondary outcome, and was significantly longer in the group receiving Anoro Ellipta compared with tiotropium in one trial[21], but not significantly different in a further two trials.[22]

Duaklir Genuair

A 24-week RCT (AFFIRM; n = 933[8]) showed significantly greater improvements in lung function (0-3 hour post-dose FEV_1) for Duaklir Genuair compared with Seretide Accuhaler 500/50. There were no significant differences between treatments for breathlessness, quality of life and exacerbations.

Two, 24-week RCTs compared Duaklir Genuair with placebo or its individual components: formoterol and aclidinium (ACLIFORM[24] COPD and AUGMENT COPD[25]). The trials evaluated 3,421 adults with COPD and a post-bronchodilator FEV_1 of 30% to 80% predicted, and reported a significantly greater improvement in lung function (1-hour post-dose FEV_1, 1-hour pre-dose FEV_1) for all comparisons. Among secondary outcomes in the published trials, Duaklir Genuair treatment showed statistically and clinically significantly greater improvement than placebo in breathlessness scores (TDI); but there was no significant difference compared with either component as monotherapy; in pooled analyses there were significantly greater improvements in TDI scores *vs.* individual components.[11] Pooled analyses of data from the ACLIFORM and AUGMENT trials also demonstrated a 29% reduction in exacerbation rate *vs*. placebo (relative risk 0.71, p = 0.036).[26]

Spiolto Respimat

A 6-week cross-over trial[27] enrolled people over 40 with moderate to severe COPD (GOLD stage 2-3) and found significantly greater improvements in lung function (FEV_1 AUC_{0-12}) for Spiolto Respimat *vs*. Seretide Accuhaler 50/500. Two 24-week RCTs compared Spiolto 5/5 µg or 2.5/2.5 µg with the individual components tiotropium (5 µg or 2.5 µg) or olodaterol 5 µg in 5,162 people aged 40 or over with moderate to very severe COPD (GOLD stage 2 to 4)[11]. Both trials reported significantly greater improvements in trough FEV_1 with the tiotropium/olodaterol combination *vs.* individual components. In two 12-week RCTs in adults with COPD (GOLD stage 2 to 3[12]), significantly greater improvements in trough FEV_1 were reported for the combination *vs*. placebo, but results were inconsistent for the combination *vs*. tiotropium as a single component; there was a significantly greater improvement in trough FEV_1 in one trial, but the difference was not statistically significant in a second.[12] All four trials reported significantly greater improvements in health-related quality of life with Spiolto Respimat *vs*. comparators.[11,12]

Adverse events

Where reported, the most common adverse events with LABA/LAMA combination inhalers were headache, nasopharyngitis and exacerbations of COPD.[21,22] Other common adverse reactions included cough and oropharyngeal pain/irritation[1,21] Reported incidences of cardiovascular events or pneumonia were not significantly different in most trials.[21,22,26] The FLAME trial[7] reported that the incidence of radiologically-confirmed pneumonia was lower with Ultibro Breezhaler (3.2%) than with Seretide Accuhaler (4.8%) (p = 0.02; NNH ~ 60 over one year's treatment with Seretide Accuhaler compared with Ultibro Breezhaler).

Considerations for the NHS

Based on Quality and Outcomes Framework data for 2014/15, the average prevalence of diagnosed COPD in subscriber CCGs is 1.81% (52,009 patients on COPD disease registers). Across the Midlands and East of England Commissioning region, the average prevalence of diagnosed COPD is 1.91% and there are 310,458 patients in COPD disease registers.

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