

**For the treatment of chronic obstructive pulmonary disease (COPD)**

**Commissioning guidance points for consideration:**

- In the 2010 [NICE guideline on the management of COPD](#), fixed-dose combination inhalers containing a long-acting  $\beta_2$  agonist (LABA) and a long-acting muscarinic antagonist (LAMA) are recommended in people who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, have FEV<sub>1</sub> less than 50% of predicted during spirometric testing and have declined or cannot tolerate an inhaled corticosteroid. LABA/LAMA inhalers are 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. The [2015 GOLD report](#) on COPD management also suggests combination LABA/LAMA treatment as an alternative after first choice treatment with LABA or LAMA in patients at low risk of exacerbations, and after ICS/LABA or LAMA treatment in patients at high risk of exacerbations.
- After consideration of the evidence for efficacy of fixed dose LABA/LAMA combination inhalers, the MTRAC committee considered that there was currently insufficient patient-oriented RCT evidence available to draw distinctions between the different products or make comparisons with LABA/ICS inhalers. [A 52-week trial](#) evaluating the Ultibro Breezhaler vs. Seretide with exacerbation rate as the primary outcome is expected to complete in September 2015.
- The committee noted that there was a saving in drug acquisition costs associated with the use of fixed-dose combination LABA/LAMA inhalers in place of the individual component medications (Ultibro Breezhaler: £242 saving per person per year; Duaklir Genuair: £97 saving per person per year; Anoro Ellipta: no calculation\*).
- Tiotropium is the longest established LAMA inhaler; a fixed dose combination product of tiotropium with olodaterol may launch this year if approved in the EU.
- The [National COPD audit programme report 2014](#) reviewed resources and organisation of care in acute NHS units in England and Wales. It recommended that acute and community providers, primary care, patient groups and commissioners should work collaboratively via local respiratory programme groups to improve coordinated care and formalise COPD pathways; respiratory specialists should take a lead in this process, forming such groups if they do not exist at present.

\* Saving cannot be determined because both components are not available as single-component inhalers

**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. Three LABA/LAMA fixed-dose combination inhalers are currently licensed for the treatment of COPD in the UK (Ultibro Breezhaler<sup>1</sup>, Anoro Ellipta<sup>2</sup>, and Duaklir Genuair<sup>3</sup>). See Table 1 overleaf for details.

**Evidence for efficacy and safety**

No systematic reviews of the efficacy or safety for the fixed-dose combination products were available at the time of review. Efficacy was assessed using fully published phase 3 RCTs that reported patient-oriented primary outcomes (exacerbations, breathlessness, health status [St George's Respiratory Questionnaire]). Where no such data were available, disease-oriented outcome (FEV<sub>1</sub>) data were reported (see Table 2 overleaf).

**Ultibro Breezhaler**

Two trials evaluated patient-oriented outcomes in adults with severe or very severe COPD (post-bronchodilator FEV<sub>1</sub> ≥ 30% and ≤ 80%<sup>4</sup>, or FEV<sub>1</sub> < 50% of predicted

normal<sup>5</sup>). Enrolled participants in the SPARK trial (n = 2,224; duration 76 weeks) had also experienced at least one prior exacerbation of COPD<sup>5</sup>. In the SPARK trial<sup>5</sup>, a 12% reduction was reported for the Ultibro Breezhaler compared with glycopyrronium for the primary outcome, which was the annualised rate of moderate or severe COPD exacerbations (number of events per patient per year). A secondary outcome, the rate of all exacerbations, was significantly lower with Ultibro compared with glycopyrronium (p < 0.0012) and open-label tiotropium (p < 0.0017).<sup>5</sup> The BLAZE trial<sup>4</sup> (n = 247; 6-week crossover study) evaluated dyspnoea (breathlessness) as the primary outcome and found significantly greater improvements with the Ultibro Breezhaler vs. placebo and tiotropium. Two further trials (ILLUMINATE<sup>6</sup>: n = 523; 26 weeks & SHINE<sup>7</sup>: n = 2,144; 26 weeks) reported a significantly greater improvement in lung function for adults using the Ultibro Breezhaler compared with Seretide<sup>6</sup> over 26 weeks' treatment in one trial; and indacaterol, glycopyrronium, open-label tiotropium and placebo in a second.<sup>7</sup>

**Anoro Ellipta**

In four, 24-week trials of adults with COPD and post-bronchodilator FEV<sub>1</sub> < 70% of predicted normal (total

*WARNING: This sheet should be read in conjunction with the Summaries of Product Characteristics. This guidance is based upon the published information available in English at the time the drugs were considered. It remains open to review in the event of significant new evidence emerging.*



n = 3,734)<sup>8-10</sup>, Anoro Ellipta treatment showed significantly greater improvement in the primary outcome of lung function (trough FEV<sub>1</sub>) than tiotropium or its individual components (vilanterol and umeclidinium). Time to first treatment exacerbation was a secondary outcome, and was significantly longer in the group receiving Anoro Ellipta compared with tiotropium in one trial<sup>8</sup>, and not significantly different in a further two trials.<sup>9</sup>

### Duaklir Genuair

Two published 24-week RCTs (ACLIFORM<sup>11</sup> COPD and AUGMENT COPD<sup>12</sup>) evaluated 3,421 adults with COPD and a post-bronchodilator FEV<sub>1</sub> between 30% and 80% of predicted normal. The trials reported a significantly greater improvement in lung function (1-hour post-dose FEV<sub>1</sub>, 1-hour pre-dose FEV<sub>1</sub>) for Duaklir treatment vs. placebo and its individual components (formoterol and acclidinium). Among secondary outcomes in the published trials, Duaklir treatment showed statistically and clinically significantly greater improvement than placebo in breathlessness scores (Transition Dyspnoea index); 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.<sup>11</sup> Pooled analyses of data from the ACLIFORM and AUGMENT trials also demonstrated a 29% reduction in exacerbation rate vs. placebo (RR 0.71, p = 0.036).<sup>13</sup>

### Adverse events

Where reported, the most common adverse events were headache, nasopharyngitis and exacerbations of COPD.<sup>8,9</sup> Other common adverse reactions included cough and oropharyngeal pain/irritation.<sup>1,8</sup> Reported incidences of cardiovascular events or pneumonia were not significantly different across treatment groups.<sup>8,9,13</sup>

### Considerations for the NHS

From QOF data for 2013/14, the average prevalence of diagnosed COPD in subscriber CCGs is 1.75% (52,741 patients on COPD disease registers). In the Midlands and East of England Commissioning region, the average prevalence of diagnosed COPD is 1.86% and there are 283,036 patients in COPD disease registers.

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

Constituents and doses licensed for COPD Brand name and <a href="#">Summary of Product Characteristics (SPC)</a>	Licensed indication	Dose <sup>a</sup> DPI: dry powder inhaler MDI: metered dose inhaler	Cost per year (excluding VAT) (Source: MIMS, <a href="#">April 2015</a> )
Indacaterol/ glycopyrronium (110 µg/50 µg) <a href="#">Ultibro Breezhaler</a> ▼ <sup>1</sup>	Maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD	DPI: One inhalation (110 µg /50 µg), once daily	£449
Vilanterol/ umeclidinium (22 µg/55 µg) <a href="#">Anoro Ellipta</a> ▼ <sup>2</sup>		DPI: One inhalation (22 µg/55 µg), once daily	£395
Formoterol/ aclidinium bromide (12 µg/340 µg) <a href="#">Duaklir Genuair</a> ▼ <sup>3</sup>		DPI: One inhalation (12 µg/340 µg), twice daily	£395

<sup>a</sup> The doses shown do not represent the full range that can be used, and they do not imply therapeutic equivalence.

**Table 2:** Summary of selected outcome evidence for efficacy from individual RCTs (See full evidence review for more detail)

	Mortality	Exacerbations	SGRQ health status	Dyspnoea	Lung Function (FEV <sub>1</sub> )
<b>Ultibro Breezhaler</b> vs. placebo <sup>4,7</sup> vs. glycopyrronium <sup>5</sup> vs. indacaterol <sup>7</sup> vs. tiotropium <sup>b 5,4,7</sup> vs. Seretide <sup>6</sup>	- - - - -	(Exacerbation rate) - ↑↑ - ↔ ↑↑ <sup>c</sup> -	- ↑↑ - ↑↑ ↔	↑ - - ↑↑ ↑↑	↑ ↑↑ ↑↑ ↑↑ ↑↑
<b>Anoro Ellipta</b> vs. placebo <sup>10</sup> vs. umeclidinium <sup>10</sup> vs. tiotropium <sup>8,9</sup>	- - -	(Time to first exacerbation) ↑ - ↔ ↑↑ <sup>8</sup>	↑ ↔ ↔ ↑↑ <sup>8</sup>	↑ ↔ ↔	↔ ↑ <sup>9</sup> ↑↑ <sup>10</sup> ↑↑
<b>Duaklir Genuair</b> vs. placebo <sup>11-13</sup> vs. aclidinium <sup>11-13</sup> vs. formoterol <sup>11-13</sup>	- - -	↑ <sup>d</sup> - -	↑↔ ↔ ↔	↑ ↑↑ <sup>d</sup> ↑↑ <sup>d</sup>	↑ ↑↑ ↑↑

Key: ↑ significantly better than placebo; ↑↑ significantly better than active comparator; ↔ no significant difference vs. placebo; ↔ No significant difference vs. active comparator; - No data available in trials reviewed.<sup>b</sup> Tiotropium: open-label in two trials and masked in a second; <sup>c</sup> no significant difference in rate for severe exacerbations and those leading to hospitalisation, significant difference in rate of all exacerbations; <sup>d</sup> from pooled data analyses in EPAR, no significant difference in individual trials

### References

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