Commissioning Support
Fixed-dose LABA/ICS inhalers:
Seretide Accuhaler, AirFluSal Forspiro, Relvar Ellipta®, Symbicort DPI & MDI, DuoResp Spiromax, Fostair, Fostair Nexthaler
For the treatment of chronic obstructive pulmonary disease (COPD)

Commissioning guidance points for consideration:
- Before stepping up treatment, a patient’s inhaler technique, compliance with administration instructions, and tolerance of the 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 a similar device as the former treatment is recommended.
- A therapeutic trial of generic products (DuoResp Spiromax, AirFluSal Forspiro) may be helpful in newly diagnosed patients or those requiring a change of therapy; in consultation with the patient.
- The 2017 GOLD report advises on the treatment of stable COPD recommends stepping up to a combination of a long-acting β2-agonist bronchodilator and a long-acting muscarinic antagonist (LABA/LAMA) inhaler as first-choice fixed-dose combination therapy (FDC), when initial treatment with a single 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 discussed. In patients with a history and/or findings suggestive of asthma/COPD overlap, LABA/ICS may be a more appropriate first choice.
- In the 2010 NICE guideline on the management of COPD, FDC inhalers containing a long-acting β2 agonist (LABA) and an inhaled corticosteroid (ICS) are recommended in people who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, and have FEV₁ less than 50% of predicted during spirometric testing. LABA/ICS inhalers are also a treatment option in people with persistent exacerbations or breathlessness despite maintenance therapy with a LABA.
- 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 combination inhaled treatments containing a LABA and an inhaled corticosteroid (LABA/ICS). Six LABA/ICS inhalers are currently licensed for the treatment of COPD in the UK (Seretide Accuhaler¹, AirFluSal Forspiro³, Relvar Ellipta⁴, Symbicort in dry powder and metered dose formulations⁵,⁶,⁹, and DuoResp Spiromax⁷,⁸, Fostair MDI¹⁰ and Fostair NEXThaler¹¹). See Table 1 overview for details.

Effectiveness:
- Mortality: Mortality rates were not significantly different with Seretide or salmeterol treatment in the TORCH trial⁴, or for Relvar vs. any comparators (vilanterol, fluticasone furoate or placebo) in the SUMMIT¹³ trial.
- Seretide-treated participants in the INSPIRE trial¹⁴ showed lower rates of mortality and greater improvements in health status than with tiotropium, but the high drop-out rate in the tiotropium group raised concerns of selection bias affecting the clinical significance of the results.

Exacerbations:
- Seretide Accuhaler was the comparator product in two trials evaluating FDC inhalers containing a LABA and a long-acting muscarinic antagonist (LAMA) in COPD patients: FLAME¹⁵ and AFFIRM¹⁶. In the FLAME trial¹⁵, lower exacerbation rates (all exacerbations, and moderate to severe exacerbations requiring hospitalisation) were reported with Ulitbro Breezhaler (indacaterol/ glycopyrronium 110 µg/50 µg) vs. Seretide Accuhaler over 52 weeks. In the AFFIRM trial¹⁶, there was no significant difference in the secondary outcome of exacerbation rate (any requiring intervention: dose adjustment, antibiotic treatment, or hospitalisation) for Duaklir Genuair (formoterol/ aclidinium bromide 12 µg/340 µg) vs. Seretide Accuhaler over 24 weeks.
- Trials evaluating Seretide¹⁴,¹⁷ reported fewer exacerbations vs. placebo treatment or the individual components (salmeterol or fluticasone propionate).
- Symbicort treatment resulted in fewer exacerbations than in patients receiving placebo or formoterol, but not budesonide¹⁸,¹⁹
- With Fostair MDI treatment²⁰, there was no significant difference in total exacerbation rate versus formoterol or Symbicort, but a higher rate of exacerbations requiring hospitalisation [low patient numbers; trial may be underpowered to test the outcome].

Safety:
- Pneumonia
  - The MHRA has advised that treatment with an ICS in COPD, either alone or in combination with a LABA, significantly increases the risk of pneumonia, but benefits of treatment continue to outweigh the risks.
  - In the FLAME trial¹⁵, 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).
  - In the TORCH trial, the probability of pneumonia was 19.6% in the fluticasone propionate/salmeterol group and 18.3% with fluticasone propionate alone compared with 12.3% in the placebo group.¹²

*Summary includes the direct head-to-head comparative trial evidence evaluating fixed-dose LABA/ICS combination inhalers vs another fixed-dose combination, placebo or monotherapy active comparators, available at the time of consideration of the evidence. Not all LABA/ICS combination inhalers have been compared in RCTs*
There was a significantly lower exacerbation rate for the Fostair NEXThaler vs. placebo24,25. In the Salford Lung study22, the rate of moderate or severe exacerbations was significantly lower for Relvar vs. usual care by 8.4% (1.74 vs. 1.9; p = 0.02). Usual care was defined as baseline COPD treatment as determined by the participant’s GP and continued during the study.

Breathlessness:
- Seretide Accuhaler 500/50 was a comparator product in a trial evaluating Anoro Ellipta (vilanterol/umeclidinium 22 µg/55 µg) and reporting breathlessness as an outcome. No significant difference was reported in Transition Dyspnoea index scores for Anoro Ellipta vs. Seretide Accuhaler 500/50.23
- One trial reported an improvement for Seretide treatment vs. salmeterol.17
- No clinically meaningful differences were reported in breathlessness scores with Relvar Ellipta vs. placebo.24,25
- No significant differences in the dyspnoea score were reported for Fostair treatment compared with Symbicort or formoterol.26

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).
- None of the trials reported quality of life as a primary outcome.

### Systematic review evidence

In a 2016 evaluation of the comparative efficacy of any combination of long-acting inhaled agents for the treatment of COPD compared with any other or placebo26, the primary outcome was the proportion of patients with moderate-to-severe exacerbations (worsening symptoms requiring oral steroids/antibiotics or hospitalisation). In a subset of data from patients with moderate-to-severe exacerbations (worsening symptoms requiring oral steroids/antibiotics or hospitalisation). In a subset of data from patients with moderate-to-severe exacerbations requiring oral steroids/antibiotics or hospitalisation. In a subset of data from patients with moderate-to-severe exacerbations requiring oral steroids/antibiotics or hospitalisation.

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<tr>
<th>Constituents and metered doses licensed for COPD</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt;, threshold specified despite regular bronchodilator therapy</th>
<th>Dose&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Current costs of LABA/ICS combined inhalers listed below (Yearly cost, excluding VAT; MIMS Online, August 2016):</th>
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<tr>
<td>Fluticasone propionate / salmeterol (500 µg/50 µg licensed for COPD) Seretide Accuhaler 500&lt;sup&gt;1&lt;/sup&gt;</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, &lt;60%</td>
<td>DPI: One inhalation, twice daily</td>
<td>£498</td>
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<tr>
<td>Fluticasone propionate / salmeterol (500 µg/50 µg licensed for COPD) AirFluSal Forspiro 50/500&lt;sup&gt;2&lt;/sup&gt;</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, &lt;60%</td>
<td>DPI: One inhalation, twice daily</td>
<td>£398</td>
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<tr>
<td>Fluticasone furoate/vilanterol (92 µg/22 µg licensed for COPD) Relvar Ellipta 92/22&lt;sup&gt;2&lt;/sup&gt; ▼</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, &lt;70%</td>
<td>DPI: One inhalation, once daily</td>
<td>£268</td>
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<tr>
<td>Budesonide/formoterol (200 µg/6 µg &amp; 400 µg/12 µg licensed for COPD) Symbicort 200/6&lt;sup&gt;3&lt;/sup&gt; and 400/12&lt;sup&gt;3&lt;/sup&gt;</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, &lt;50%</td>
<td>DPI: Two inhalations of 200 µg /6 µg twice daily or one inhalation of 400 µg /12 µg twice daily</td>
<td>£462</td>
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<td>Budesonide/formoterol (160 µg/4.5 µg &amp; 320 µg/9 µg licensed for COPD) DuoResp Spiromax 160/4.5&lt;sup&gt;7&lt;/sup&gt; and 320/9&lt;sup&gt;8&lt;/sup&gt;</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, &lt;50%</td>
<td>DPI: Two inhalations of 160 µg /4.5 µg twice daily or one inhalation of 320 µg /9 µg twice daily</td>
<td>£365</td>
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<tr>
<td>Budesonide/formoterol 200 µg/6 µg Symbicort 200/6&lt;sup&gt;9&lt;/sup&gt;</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, &lt;70%</td>
<td>MDI: Two inhalations, twice daily</td>
<td>£341</td>
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<tr>
<td>Beclometasone/formoterol (100 µg/6 µg) Fostair&lt;sup&gt;10&lt;/sup&gt; and Fostair NEXThaler&lt;sup&gt;11&lt;/sup&gt;</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, &lt;50%</td>
<td>Fostair MDI: Two inhalations, twice daily Fostair NEXThaler DPI: Two inhalations, twice daily</td>
<td>£357</td>
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<sup>a</sup>The doses shown do not represent the full range that can be used, and they do not imply therapeutic equivalence; doses described are metered dose or delivered dose (actual dose leaving mouthpiece) as per the SPC. AirFluSal Forspiro equivalent to Seretide Accuhaler 500; DuoResp Spiromax 160/4.5 and 320/9 equivalent to Symbicort 200/6 and 400/12 respectively.

<sup>b</sup>Delivered dose
on all-cause mortality in people with COPD found a reduction in total mortality of 20% associated with use of a LABA/ICS combination inhaler (Seretide or Symbicort) versus placebo; whereas single-component LABAs or tiotropium did not alter mortality. These conclusions were not affected by the inclusion or exclusion of data from the TORCH and UPLIFT trials, two large longer-term trials of 3 and 4 years’ duration, respectively, which evaluated mortality in patients with COPD treated with Seretide or tiotropium vs. placebo. In pooled data from 17 trials of Seretide or Symbicort vs. placebo, Seretide vs. tiotropium (one trial) or Seretide vs. salmeterol a total of 269 deaths were reported in LABA/ICS arms (n = 6,766) compared with 333 deaths in the reference group (all comparators; n = 6,482).

**Adverse events: focus on pneumonia**

A review of ICS-containing products used in the treatment of COPD published by the European Medicines Agency Pharmacovigilance Risk Assessment Committee (PRAC) confirmed the earlier MHRA report in 2009 that there is an increased risk of pneumonia with the use of ICS-containing treatments; but that the benefits of treatments continue to outweigh the risks.

**References**

6. AstraZeneca UK Limited, Symbicort Turbuhaler 400/12, Inhalation powder, EMC 2016.
8. Teva Pharma B.V. DuoResp Spiromax 320 micrograms/9 micrograms inhalation powder. EMC 2016.

Guidance on the use of ICS in people with COPD, reminded healthcare professionals that ICS should not be used alone in COPD. A post-hoc analysis of data from the TORCH trial estimated one extra case of pneumonia for every 31 patients treated with Seretide vs. placebo every year. The FLAME trial 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). The Salford Lung Study found a similar incidence of serious adverse events listed as pneumonia in groups receiving Relvar or usual care (incidence ratio, 1.1; 95% CI, 0.9 to 1.5).

**Considerations for the NHS**

Based on QOF 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.

29. Cave AC, Hurst MM. The use of long-acting ß2-agonists, alone or in combination with inhaled corticosteroids, in Chronic Obstructive Pulmonary Disease (COPD) - A risk-benefit analysis. Pharmacology & Therapeutics 2011; 130:114-143.