MTRAC
Midlands Therapeutics Review and Advisory Committee

Commissioning Support
Fixed-dose LABA/ICS inhalers:

DuoResp Spiromax® 160/4.5 & 320/9, Fostair 100/6 MDI®, Relvar Ellipta®▼ 92/22, Seretide Accuhaler®, Symbicort Turbohaler® 200/6 & 400/12

For the treatment of chronic obstructive pulmonary disease (COPD)

Commissioning guidance points for consideration:

- In the NICE guideline on the management of COPD, fixed-dose combination inhalers containing a long-acting ß$_2$ 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 FEV_1 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.
- After consideration of the evidence for efficacy of LABA/ICS fixed-dose combination inhalers, the MTRAC committee considered that the established products Seretide Accuhaler (salmeterol/fluticasone propionate) and Symbicort Turbohaler (formoterol/budesonide) had the largest evidence base for efficacy.
- Evidence for Fostair was also considered relatively strong in that it was shown to be non-inferior to the established LABA/ICS products: Symbicort in one RCT (outcome: exacerbation rate, 48-week trial) and Seretide Accuhaler in a second (outcome: breathlessness and lung function [FEV_1], 12-week trial). Fostair is formulated from well-established component medications (formoterol and beclometasone) and has a lower acquisition cost that some of the other products in this class.
- The evidence for the Relvar Ellipta inhaler (vilanterol/fluticasone furoate) was considered relatively weak. Comparative evidence against Seretide 250 mcg twice daily from three 12-week RCTs reported in a single article found significantly greater improvement in lung function in one trial but not in a further two. Pooled analyses of data from the three trials found a significantly greater improvement with Relvar Ellipta. There were no comparative data for exacerbation rate or other patient-oriented outcomes against placebo or other LABA/ICS inhalers.
- The committee also noted that a generic version of Symbicort (DuoResp Spiromax) was launched in December 2014 but published RCT evidence for efficacy was not available. Bioequivalence to Symbicort was demonstrated in the assessment report for licensing.[3] The price of the DuoResp Spiromax is £365 per patient per year, a saving of £97 per patient *vs.* Symbicort Turbuhaler.
- 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.

Description of the technology

This overview is concerned with fixed-dose LABA/ICS combination inhaled treatments containing a long-acting bronchodilator and an anti-inflammatory agent for the maintenance treatment of COPD. There are currently five LABA/ICS combination inhalers licensed for the treatment of COPD in the UK (DuoResp Spiromax[6], Fostair 100/6 MDI[4], Relvar Ellipta[5], Seretide Accuhaler[2], Symbicort Turbohaler[1]). The licensed indications and doses are shown in Table 1 overleaf.

Systematic review evidence

Effect of LABA/ICS on total mortality

A 2010 systematic review[7] of the effect of LABA/ICS on all-cause mortality in people with COPD found a reduction in total mortality of 20% associated with use of an LABA/ICS combination inhaler (Seretide or Symbicort); 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[8] and UPLIFT[9] 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).

Incidence of pneumonia

A 2009 MHRA risk:benefit review[10] of LABA/ICS combination inhalers concluded that the overall benefits of LABAs, both as monotherapy and in combination with ICS, in the treatment of COPD continued to outweigh any risks. Healthcare professionals were reminded that ICS should not be used alone in COPD. A key issue remains the increased risk of pneumonia associated with the use of ICS in COPD.[11] A *post-hoc* analysis of data from the TORCH trial estimated one extra case of pneumonia for every 31 patients treated

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with Seretide every year.[12] A 2011 systematic review[13] determined the relative incidence of pneumonia adverse events, pneumonia serious adverse events and pneumonia-related mortality in patients with COPD treated with Symbicort or Seretide using indirect analyses. The review reported a significant benefit in favour of Symbicort for the proportions of patients experiencing a pneumonia adverse event (OR 0.47; 95% CI 0.28 to 0.80), or pneumonia serious adverse event (OR 0.41; 95% CI 0.19 to 0.86) compared with Seretide treatment.

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/ICS combination inhalers available in the UK

Constituents and doses (ICS/LABA) licensed for COPD **Brand name and Summary of Product Characteristics (SPC)**	**FEV_1 threshold specified in licensed indication**	**Also indicated for asthma?**	**Dose[a]** DPI: dry powder inhaler MDI: metered dose inhaler	**Cost per year (excluding VAT)** **(Source: MIMS, April 2015)**	**Patent expiry year[b]**
Budesonide/ formoterol (200 µg/6 µg & 400 µg/12 µg) Symbicort 200/6 and 400/12[1]	FEV_1 <50% with exacerbation history despite regular long-acting bronchodilator therapy.	YES	DPI: Two inhalations of 200 µg /6 µg twice daily or one inhalation of 400 µg /12 µg twice daily	£462	Expired
Fluticasone propionate/ salmeterol (500 µg/50 µg) Seretide Accuhaler 500[2]	FEV_1 <60%, and a history of repeated exacerbations despite regular long-acting bronchodilator therapy.	YES	DPI: One inhalation twice daily.	£498	Expired
Beclometasone/ formoterol (100 µg/6 µg) Fostair 100/6[4]	FEV1 < 50% with exacerbation history despite regular long-acting bronchodilator therapy.	YES	MDI: Two inhalations, twice daily	£357	2021*
Fluticasone furoate/vilanterol (92 µg/22 µg) Relvar Ellipta 92/22▼[5]	FEV_1 <70%, with exacerbation history despite regular long-acting bronchodilator therapy.	YES	DPI: One inhalation, once daily	£338	2023†
Budesonide/ formoterol (200 µg/6 µg & 400 µg/12 µg) DuoResp Spiromax 160/4.5 and 320/9[6]	FEV_1 <50% with exacerbation history despite regular long-acting bronchodilator therapy.	YES	DPI: Two inhalations of 160 µg /4.5 µg twice daily or one inhalation of 320 µg /9 µg twice daily	£365	Generic

[a] *Doses listed do not represent the full range available, and not imply therapeutic equivalence.*
[b] *Patent expiry dates estimate the earliest possible date of a potential generic product and are subject to change; *Patent expiry dates reported in UKMi Patents expiry database; † Patent expiry dates estimated from SPC dates.*

Table 2: Summary of selected evidence for efficacy from individual RCTs *(see full evidence summary for detail)*

	Mortality	**Exacerbations**	**SGRQ health status**	**Dyspnoea**	**Lung Function (FEV_1)**
Symbicort Turbohaler					*(post-dose)*
vs. placebo[14,15]	-	↑	↑	-	↑
vs. formoterol[14,15]	-	↑↑	↔	-	↔
Seretide Accuhaler					*(post-dose)*
vs. placebo[8]	↔	↑	↑	-	↑
vs. salmeterol[8,16]	↔	↑↑	↑↑	↑↑	↔
vs. tiotropium[17]	↑↑[c]	↔	↑↑	-	↔
Fostair 100/6 MDI					
vs. placebo	-	-	-	-	-
vs. formoterol[18,19]	-	↑↑	↑↑	↔	↑↑ *(pre-dose)*
vs. Symbicort[d,18]	-	↔	↔	↔	↔ *(pre-dose)*
vs. Seretide[20]	-	-	↔	-	↑↑ *(post-dose)*
Relvar Ellipta					↑ *(post-dose)*[22]
vs. placebo[21]	-	-	-	↔	↔[22] ↑↑[23e]
vs. Seretide[22,23]	-	-	-	-	*(weighted mean 24-hour measurement)*
(LABA single component not licensed)					

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.
[c] *Clinical significance unclear, high risk of selection bias;* [d] *Non-inferiority trial;* [e] *Significantly greater improvement vs. Seretide in 1/3 trials, but pooled data showed significant result overall*

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