MTRAC
Midlands Therapeutics Review and Advisory Committee

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[2] advice on the treatment of stable COPD recommends stepping up to a combination of a long-acting ß$_2$-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.[2]
- In the 2010 NICE guideline on the management of COPD, FDC inhalers containing a long-acting ß2 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.
- 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 Accuhaler[1], AirFluSal Forspiro[3], Relvar Ellipta▼[4], Symbicort in dry powder and metered dose formulations[5,6,9], and DuoResp Spiromax[7,8], FostairMDI[10] and Fostair NEXThaler[11]). See Table 1 overleaf for details.

Effectiveness:[a]

Mortality:

- Mortality rates were not significantly different with Seretide or salmeterol treatment in the TORCH trial[12], or for Relvar *vs*. any comparators (vilanterol, fluticasone furoate or placebo) in the SUMMIT[13] trial.
- Seretide-treated participants in the INSPIRE trial[14] 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: FLAME[15] and AFFIRM[16]. In the FLAME trial[15], lower exacerbation rates (all exacerbations, and moderate to severe exacerbations requiring hospitalisation) were reported with Ultibro Breezhaler (indacaterol/ glycopyrronium 110 µg/50 µg) *vs*. Seretide Accuhaler over 52 weeks. In the AFFIRM trial[16], 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 Seretide[14,17] 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 budesonide.[18,19]
- With Fostair MDI treatment[20], 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 trial[15], 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]

[a]*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*. formoterol in the FORWARD trial.[21] • .In the Salford Lung study[22], 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 MDI treatment compared with Symbicort or formoterol.[20]	***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 placebo[26], 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 a prior exacerbation, Seretide, Symbicort and the LABA/LAMA Ultibro Breezhaler were all found to have a lower exacerbation rate *vs*. placebo. Among secondary outcomes, Seretide was shown to have a significantly lower risk *vs*. placebo for overall mortality. The incidence of pneumonia was shown to be significantly higher with Seretide *vs*. placebo, but not significantly different for Symbicort, Relvar, Fostair Nexthaler or for the LABA/LAMAs – Ultibro and Anoro. In sensitivity analyses, both Seretide and Symbicort were found to have a greater risk of pneumonia than placebo.[26]

A 2010 systematic review[27] of the **effect of LABA/ICS**

Table 1: Details of fixed-dose LABA/ICS combination inhalers available in the UK; all products are licensed for use as maintenance bronchodilator treatments to relieve symptoms in adult patients with COPD; see SPCs for details of specific licensed indications

Constituents and metered doses[a] licensed for COPD **Brand name and Summary of Product Characteristics (SPC)**	**FEV_1 threshold specified** despite regular bronchodilator therapy	**Dose[a]** DPI: dry powder inhaler MDI: metered dose inhaler	**Current costs** of LABA/ICS combined inhalers are listed below (Yearly cost, excluding VAT; MIMs Online, August 2016):
Fluticasone propionate / salmeterol (500 µg/50 µg licensed for COPD) Seretide Accuhaler 500[1]	FEV_1<60%	DPI: One inhalation, twice daily.	£498
Fluticasone propionate / salmeterol (500 µg/50 µg licensed for COPD) AirFluSal Forspiro 50/500[3]	FEV_1<60%	DPI: One inhalation, twice daily.	£398
Fluticasone furoate/vilanterol (92 µg/22 µg[b] licensed for COPD) Relvar Ellipta 92/22[4] ▼	FEV_1<70%	DPI: One inhalation, once daily.	£268
Budesonide/formoterol (200 µg/6 µg & 400 µg/12 µg licensed for COPD) Symbicort 200/6[5] and 400/12[6]	FEV_1<50%	DPI: Two inhalations of 200 µg /6 µg twice daily or one inhalation of 400 µg /12 µg twice daily	£462
Budesonide/formoterol (160 µg/4.5 µg[b] & 320 µg/9 µg[b] licensed for COPD) DuoResp Spiromax 160/4.5[7] and 320/9[8]	FEV_1<50%	DPI: Two inhalations of 160 µg /4.5 µg twice daily or one inhalation of 320 µg /9 µg twice daily	£365
Budesonide/formoterol 200 µg/6 µg Symbicort 200/6[9]	FEV_1<70%	MDI: Two inhalations, twice daily	£341
Beclometasone/formoterol (100 µg/6 µg) Fostair[10] and Fostair NEXThaler[11]	FEV_1<50%	Fostair MDI: Two inhalations, twice daily Fostair NEXThaler DPI: Two inhalations, twice daily	£357

[a] *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.*

[b] *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[12] and UPLIFT[28] 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[29] that there is an increased risk of pneumonia with the use of ICS-containing treatments; but that the benefits of treatment continue to outweigh the risks.

Guidance on the use of ICS in people with COPD[30], 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.[31] The FLAME trial[15] 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 lsted as pneumonia in groups receiving Relvar or usual care (incidence ratio, 1.1; 95% CI, 0.9 to 1.5).[22]

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.

References

1. GlaxoSmithKline UK. Seretide 100, 250, 500 Accuhaler. 2017
2. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017.
3. Sandoz Ltd. AirFluSal Forspiro 50 microgram/500 microgram per actuation inhalation powder, pre-dispensed. EMC 2016
4. GlaxoSmithKline UK. Relvar Ellipta 92 micrograms/22 micrograms inhalation powder. EMC 2016
5. AstraZeneca UK Limited. Symbicort Turbohaler 200/6 Inhalation powder. EMC 2016
6. AstraZeneca UK Limited. Symbicort Turbohaler 400/12, Inhalation powder. EMC 2016
7. Teva Pharma B.V. DuoResp Spiromax 160 micrograms / 4.5 micrograms inhalation powder. EMC 2016
8. Teva Pharma B.V. DuoResp Spiromax 320 micrograms/9 micrograms inhalation powder. EMC 2016
9. AstraZeneca UK Limited. Symbicort, 200 micrograms/6 micrograms per actuation, pressurised inhalation, suspension. EMC 2016
10. http://www.medicines.org.uk/emc/medicine/21006
11. Chiesi Ltd. Fostair NEXThaler 100/6. EMC 2016
12. Calverley PM et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356(8):775-789.
13. Vestbo J et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet* 2016; 387(10030):1817-1826.
14. Wedzicha JA et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008; 177(1):19-26.
15. Wedzicha JA al. Indacaterol–Glycopyrronium versus Salmetero-Fluticasone for COPD. *N Engl J Med* 2016; 374(23):2222-2234.
16. Vogelmeier C et al. Efficacy and safety of aclidinium/formoterol versus salmeterol/fluticasone: a phase 3 COPD study. *Eur Respir J* 2016.
17. Kardos P et al. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 175(2):144-149.
18. Calverley PM et al. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J* 2003; 22(6):912-919.
19. Szafranski W et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J* 2003; 21(1):74-81.
20. Calverley PM et al. Beclomethasone/formoterol in the management of COPD: a randomised controlled trial. *Respir Med* 2010; 104(12):1858-1868.
21. Wedzicha JA et al. Extrafine beclomethasone/formoterol in severe COPD patients with history of exacerbations. *Respir Med* 2014; 108(8):1153-1162.
22. Vestbo J et al. Effectiveness of Fluticasone Furoate–Vilanterol for COPD in Clinical Practice. N Engl J Med 2016 375:[1253-1260] http://www.nejm.org/doi/full/10.1056/NEJMoa1608033
23. Singh D et al. Umeclidinium/vilanterol versus fluticasone propionate/salmeterol in COPD: a randomised trial. BMC Pulm Med 2015 15:[91]
24. Kerwin EM et al. A randomised trial of fluticasone furoate/vilanterol (50/25 mug; 100/25 mug) on lung function in COPD. *Respir Med* 2013; 107(4):560-569.
25. Martinez FJ et al. Fluticasone furoate/vilanterol (100/25; 200/25 mug) improves lung function in COPD: a randomised trial. *Respir Med* 2013; 107(4):550-559.
26. Tricco AC et al. Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis. *BMJ Open* 2015; 5(10):e009183.
27. Kliber A, Lynd LD, Sin DD. The effects of long-acting bronchodilators on total mortality in patients with stable chronic obstructive pulmonary disease. *Respir Res* 2010; 11:56.
28. Burgel PR, Paillasseur JL, Dusser D, Roche N, Liu D, Liu Y et al. Tiotropium might improve survival in subjects with COPD at high risk of mortality. *Respir Res* 2014; 15:64.
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.
30. Use of long-acting ß-agonists in chronic obstructive pulmonary disease. Drug Safety Update 2009 2:[7]
31. Crim C et al. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. *Eur Respir J* 2009; 34(3):641-647.

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Date: September 2016