MTRAC
Midlands Therapeutics Review and Advisory Committee

Considerations for Commissioners
Fixed-dose combination ICS/LABA inhalers

(DuoResp Spiromax, flutiform, Fostair 100/6, Fostair100/6 NEXThaler, Relvar Ellipta▼, Sirdupla)

For the treatment of asthma

Commissioning considerations for the use of ICS/LABA inhalers for asthma:

- The choice of inhaled corticosteroid/long-acting ß$_2$-agonist (ICS/LABA) combination inhaler should be the product and type of inhaler device with the lowest acquisition cost that is suitable for the person, and in agreement with their preferences.
- The NICE Quality Standard on asthma (QS25, 2013), advises that people with asthma are given specific training and assessment in inhaler technique before starting any new inhaler treatment.
- As with other products licensed for once-daily use, take measures to ensure people are aware of the hazards of accidental overdose if the Relvar Ellipta inhaler is taken twice daily.
- There are good opportunities to review the choice of ICS/LABA inhaler during any initiation of treatment, and when stepping up or stepping down treatment.
- Take steps to avoid **inadvertent** switching from the person's current inhaler to a generic version.
- Take into account issues raised in the national review of asthma deaths :
    - Excessive prescribing of short-acting reliever inhalers (> 12 inhalations of salbutamol/day)
    - Under-prescribing of a steroid-based preventer inhaler
    - Inappropriate prescribing of a LABA without concomitant inhaled corticosteroid

Strength of the evidence for efficacy

The strength of the RCT (randomised controlled trial) direct head-to-head evidence for efficacy between ICS/LABA inhalers was considered to be relatively weak in that the primary outcomes measured were disease-oriented measures of lung function rather than patient-oriented measures (premature death, exacerbations, quality of life) and the duration of the trials was short for a chronic disease.

Description of technology

This overview is concerned with the newer fixed dose ICS/LABA inhaler combinations for the treatment of asthma.

Since the launch of Seretide and Symbicort, there have been five ICS/LABA combination inhalers licensed for the treatment of asthma in the UK (DuoResp Spiromax, Flutiform, Fostair, Relvar Ellipta and Sirdupla).

The products are all indicated for the regular treatment of asthma where use of a combination product (LABA and ICS) is appropriate*:

- patients not adequately controlled with ICS and 'as needed' inhaled short-acting β_2 agonist OR
- patients already adequately controlled on both ICS and LABA (not Relvar Ellipta).

(use as maintenance and reliever therapy [MART] was outside the remit of this review)*

MTRAC has produced individual guidance sheets for flutiform for the treatment of asthma, and Relvar Ellipta for the treatment of asthma and COPD.

Background

About 5.4 million people in the UK are currently receiving treatment for asthma: 1.1 million children (1 in 11), and 4.3 million adults (1 in 12).[1]

NICE guidance (TA 138; 2008) on the use of ICS in adults and children aged 12 years and over, recommends use of a combination inhaler device as an option in patients in whom treatment with an ICS and LABA is considered appropriate.[2] If a combination device is chosen, then the least costly device that is suitable for the individual is recommended.[2]

In the BTS/SIGN guidance on asthma (updated 2014), the use of combination inhalers is recommended to improve inhaler adherence, and guarantee that the LABA is not taken without an inhaled steroid.[3]

Systematic review evidence for efficacy and safety

There were no published systematic reviews that evaluated any of the newer ICS/LABA products.

One 2011 Cochrane review[4] reported rates of exacerbations of asthma in participants treated with Seretide or Symbicort (from 5 trials; 5,537 participants), and found slightly lower odds of an exacerbation with Seretide *vs.* Symbicort, and slightly higher odds of hospitalisation but neither result reached statistical significance. There was also no statistically significant difference between the treatments for the rates of serious adverse events.

A second review of 89 trials[5] pooled analyses of any ICS/LABA *vs*. placebo or same-dose ICS monotherapy. A sub-analysis of ICS/LABA combinations *vs*. same-dose ICS monotherapy (25 studies with 11,269 adults) found that absolute differences in mortality were very small, translating into an increase of 3 per 10,000 over 32 weeks on any combination therapy (95% confidence interval [CI] 3 less to 17 more) compared with placebo or ICS monotherapy.

No significant difference in all-cause mortality was found between formoterol and salmeterol combination therapy

from the few trials that directly compared the two treatments (Odds Ratio [OR] 2.68, 95% CI 0.44 to 16.14,10 studies, n = 6,769).

Evidence from direct head-to-head trials of combination products showed no significant differences between formoterol and salmeterol for the incidence of non-fatal SAEs of any cause (OR 0.69, 95% CI 0.37 to 1.26, 8 studies, n = 6,163).[5]

RCTs: Individual products *vs.* Seretide or Symbicort

This review focussed on phase 3 active comparator trials that evaluated the superiority or non-inferiority of newer treatments to Seretide or Symbicort (current established treatments).

Seretide as comparator

Two of the newer ICS/LABA inhalers were shown to be non-inferior to Seretide in head to head trials evaluating lung function: Flutiform[6] and Fostair 100/6[7,8]. In a third trial[9], Relvar was not significantly different than Seretide for the same outcome. All the trials were of 12 or 24-weeks duration with disease-oriented outcomes: the mean change in pre-dose FEV_1 (forced expiratory volume in 1 second [FEV_1]) from baseline to the 12-week end of the study for Flutiform[6], mean change in the last 2 weeks of a 12-week treatment period in morning PEF (peak expiratory flow) for Fostair[7,8], and mean 0-24 hour FEV_1 after 24 weeks for Relvar[9].

Symbicort as comparator

Three trials reported that Flutiform, Fostair 100/6 and DuoResp inhalers were non-inferior for changes in lung function when compared with Symbicort. Two of the trials were non-inferiority trials of 12 weeks duration that evaluated Flutiform[10] and Fostair 100/6[11], and the third was a poster presentation that reported the non-inferiority of DuoResp to Symbicort[12]. Again, the outcomes reported were disease-oriented: average daily trough morning PEF and trough FEV_1 over 12 weeks for DuoResp[12], the mean change in pre-dose FEV_1 from baseline the end of the trial for Flutiform[10], and mean change in the last 2 weeks of a 12-week treatment period in morning PEF for Fostair. [11]

Adverse events

The most frequent adverse events reported across the trials were headache, nasopharyngitis and oropharyngeal candidiasis; exacerbations of asthma were also reported. Summaries of Product Characteristics (SPCs) advise caution in patients with respiratory tract infections, and in patients with co-existing risk factors for osteoporosis.

Adrenal suppression is one of a number of side effects associated with use of systemic corticosteroids, and hypokalaemia, and prolongation of the QT interval in at-risk patients are associated with long-acting $ß_2$-agonist therapy.

Considerations for cost impact

In prevalence data from the 2014/15 Quality and Outcomes Framework[13], there are 1,063,939 people in the Midlands and East of England commissioning region registered in GP records as receiving treatment for asthma.

Table: Doses and costs for preventer use in asthma for the ICS/LABA combination inhalers ***(hyperlinks are to SPCs)***

Product name	Metered dose /mcg[a]	Eligible recipients	Cost per patient per year[b]
DuoResp Spiromax DPI (Budesonide/ formoterol)	200/6	Adults	£182 to £365
	400/12[†]		£365 to £729
Flutiform pMDI (Fluticasone propionate/ formoterol)	50/5	50/5 and 125/5 inhalers: Adults and adolescents over 12	£175
	125/5		£341
	250/10	250/10 inhaler: adults only	£554
Fostair pMDI (Beclometasone/ formoterol)[c]	100/6	Adults	£178 to £357
	100/6 Nexthaler		£178 to £357
Relvar Ellipta DPI[††] (Fluticasone furoate/vilanterol)	92/22[d]	Adults and adolescents over 12	£268
	184/22[d]		£359
Seretide pMDI (Fluticasone propionate/ salmeterol)	50/25	Adults and adolescents over 12, children > 4 years (100/50 inhaler only)	£219
	125/25		£426
	250/25		£724
Seretide DPI[†] (Fluticasone propionate/ salmeterol)	100/50		£219
	250/50		£426
	500/50		£498
Sirdupla pMDI (Fluticasone propionate/ salmeterol)	125/25	Adults	£319
	250/25		£543
Symbicort DPI (Budesonide/ formoterol)	*100/6*	Adults and adolescents over 12, children > 6 years (100/6 inhaler only)	£201 to £402
	200/6		£231 to £462
	400/12[†]		£462 to £925

[Prices from MIMS, May 2016; doses shown do not imply therapeutic equivalence; pMDI, pressurised metered dose inhaler; DPI, dry powder inhaler; devices deliver 120 doses unless stated otherwise: [†]60-dose unit; [††]30-dose unit]; [a]Twice daily doses except Relvar, which is once daily; [b]rounded to nearest pound, [c]Fostair 200/6 was not available when this evidence was considered; [d]delivered dose

References

1. Asthma facts and FAQs 2014
2. TA138 Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over. NICE 2008
3. BTS/SIGN Asthma Guideline 2014.
4. Lasserson TJ *et al. Cochrane Database Syst Rev* 2011;(12):CD004106.
5. Cates CJ *et al. Cochrane Database Syst Rev* 2014; 2:CD010314.
6. Bodzenta-Lukaszyk A *et al. BMC Pulm Med* 2011; 11:28.
7. Papi A *et al. Allergy* 2007; 62(10):1182-1188.
8. Papi A *et al. Respir Res* 2012; 13:54.
9. Woodcock A H *et al. Chest* 2013; 144(4):1222-1229.
10. Bodzenta-Lukaszyk A. *et al. J Asthma* 2012; 49(10):1060-1070.
11. Papi A *et al. Eur Respir J* 2007; 29(4):682-689.
12. Poster 227: Efficacy and safety of budesonide-formoterol (BF) Spiromax® in adults and adolescents with asthma: randomised comparison with BF Turbuhaler®. BTS Winter Meeting; 14 Dec 3; 2014.
13. Quality and Outcomes Framework (QOF) - 2014-15. HSCIC

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