

DRUG UPDATE

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STEROID/LONG-ACTING BETA₂ AGONIST COMBINATION INHALERS IN ASTHMA AND COPD

Inhaled steroid and a long acting beta₂ agonist combination inhalers are no more effective than their component inhalers used separately and there is no evidence to suggest that such inhalers improve concordance. The basic NHS cost of a combination inhaler is the same or lower than that of the separate inhalers. However, dose adjustment may be difficult with a combination inhaler and necessitate the use of additional separate inhalers, which may increase costs. Combination inhalers should therefore be reserved for patients stabilised on the component drugs in the same dose ratio.

What are they?

The combination of an inhaled steroid and long acting beta₂ agonist is appropriate for some patients with asthma and combination inhalers have been developed with the aim of improving concordance. The products currently available are Seretide® (fluticasone and salmeterol) and Symbicort® (budesonide and formoterol)

COMBINATION INHALERS IN ASTHMA

When should long-acting beta₂ agonists be used?

The 2004 BTS/SIGN guideline on the management of asthma recommends that a long-acting bronchodilator should be added at Step 3, when regular administration of an inhaled steroid (up to 800 mcg/day beclometasone or equivalent in adults or 400 mcg/day in children over 5) is insufficient.¹ This is preferred to increasing the dose of inhaled steroid. However, incomplete adherence, poor inhaler technique and trigger factors should be excluded first.

What are the benefits of combined therapy?

Compared with placebo or increasing the dose of an inhaled steroid, adding an inhaled long-acting beta₂ agonist improves asthma symptoms and lung function and reduces nocturnal waking and use of rescue medication.²

Is a combined product more effective?

Four randomised trials lasting 12 - 28 weeks compared Seretide® with fluticasone and salmeterol via separate inhalers (fluticasone/salmeterol doses were 100/50, 250/50 and 500/50 mcg twice daily) in a total of 1375 children and adults.³⁻⁶ One of these trials was carried out in 257 children aged 4 - 11.⁶ In two trials, asthma severity was consistent with current criteria for treatment at Step 3^{3,6} and, in the others, patients were taking high doses of inhaled steroids. Endpoints included change in PEF, FEV₁, asthma symptom score and use of a short-acting beta-agonist as rescue therapy. Overall, neither the efficacy nor the safety of combination and separate inhalers differed significantly.

A meta-analysis of these four studies concluded that a combination inhaler was associated with a significantly greater increase in morning peak flow than separate inhalers.⁷ However, the difference was small (5.4 L/min) and of doubtful clinical significance. This change was independent of age.

A 12-week randomised trial in 362 adults with asthma compared Symbicort® (budesonide 320 mcg, formoterol 9 mcg) twice daily with budesonide 400 mcg and formoterol 9 mcg twice daily via

separate inhalers.⁸ At study end there were no significant differences between the combined and separate inhalers with respect to changes in PEF, asthma symptom score, nocturnal waking, the number of days symptom-free or on which asthma was controlled, the use of a rescue medication or adverse events.

Adjusting the dose

Long-acting bronchodilators should be discontinued if symptoms do not improve.¹ If asthma is controlled, the dose of the steroid and bronchodilator should be stepped down to the lowest effective dose. There is no evidence on how best to achieve this asthma control, the risk of adverse effects, the benefits of treatment and patient preference should be taken into account when deciding to step down. Asthma may deteriorate at different rates in different patients therefore the steroid dose should be reduced by 25 - 50% every 3 months with regular review.¹

Using separate inhalers allows the clinician to tailor the dose of each drug to the patient's requirements. With a fixed dose inhaler dose adjustment may be difficult and necessitate the use of additional separate inhalers; this may be wasteful and increase costs.

How safe are they?

The adverse effects of combined therapy are similar to those of the component drugs. A randomised trial in 3,421 patients with asthma showed that adding a long-acting beta₂ agonist reduces the dose of inhaled steroid at which treatment targets can be achieved⁹. In this study, the overall adverse event rates associated with salmeterol/fluticasone and fluticasone alone were similar and the incidence of candidiasis or hoarseness was no lower with combined therapy than with steroid monotherapy.

COMBINED INHALERS IN COPD

When should they be used?

The NICE guideline for COPD states that a long-acting bronchodilator should be prescribed for patients who are symptomatic despite use of a short-acting bronchodilator and for those experiencing two or more exacerbations per year.¹⁰ Those who remain symptomatic despite monotherapy may benefit from combination therapy with different types of bronchodilator (e.g. a beta₂ agonist and an anticholinergic agent) or a long-acting beta₂ agonist and an inhaled steroid. Patients with severe COPD (FEV₁ = 50%) who have two more exacerbations requiring treatment with antibiotics or oral steroids per year may benefit from treatment with an inhaled steroid (none are licensed as monotherapy for this indication).

What are the benefits of combined therapy?

Compared with monotherapy with an inhaled steroid or a long-acting beta₂ agonist, a combination of the two drugs improves lung function (FEV₁) and reduces breathlessness; Symbicort®, but not Seretide®, has been shown to reduce exacerbations compared with monotherapy with its component drugs.¹¹

How do they compare?

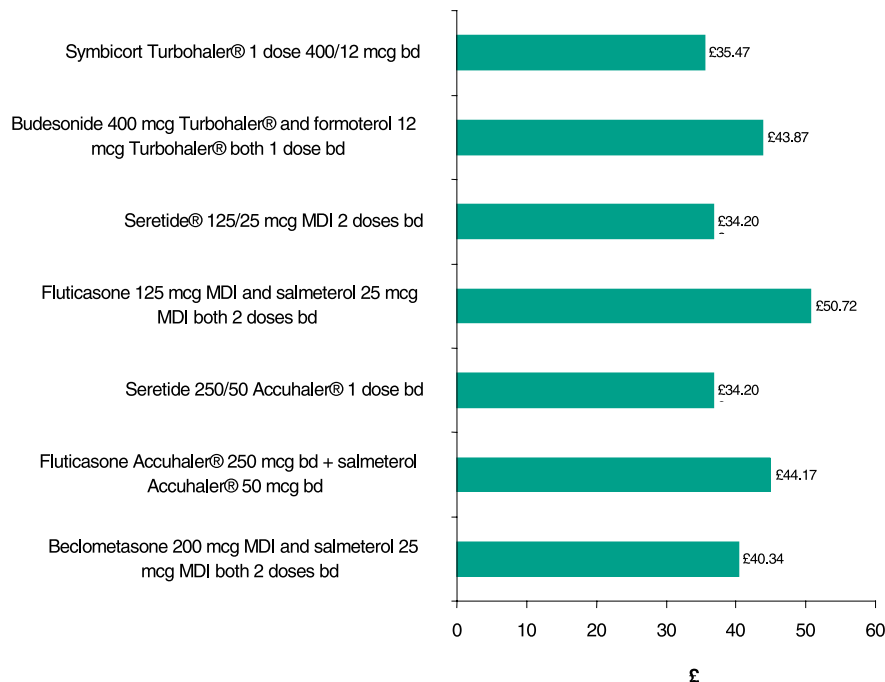
No studies comparing the efficacy and safety of, or adherence with, combined and separate bronchodilator and steroid inhalers in patients with COPD have been published. There is no guidance on steroid dose adjustment in patients with COPD. Combination therapy should be discontinued if there is no improvement after 4 weeks.¹⁰

DO COMBINATION INHALERS IMPROVE ADHERENCE?

There is no direct evidence to suggest that combination inhalers

How much do they cost?

Cost for 28 days' treatment (prices from MIMS February 2005 / BNF February 2005)



MDI metered dose inhaler. NB In clinical practice, budesonide and beclometasone are approximately equipotent; fluticasone has equal clinical activity at approximately half the dose¹. Doses shown are for general comparison only and do not imply therapeutic equivalence.

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KEY RCT - randomised controlled trial, MA-meta analysis, R-review, G - guideline

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