

Asthma focus

This bulletin focuses on inhaled treatments for asthma and reviews evidence and place in therapy for different products available and provides advice and guidance on improving care for asthma patients. This bulletin and support materials cover the following:

- Ensuring patients are reviewed and high risk patients identified and assessed.
- Ensuring stepping up and down of treatment is done in line with the British Thoracic Society (BTS) guidelines.
- Reviewing patients and stepping down high dose inhaled corticosteroid (ICS)/long acting beta agonist (LABA) combination inhalers to moderate dose ICS/LABA inhalers including an evidence review and cost analysis of available therapies (this bulletin will update and replace the current ICS/LABA PrescQIPP asthma bulletins, B5, B6, B7 and B23).
- Inhaler technique assessment.
- Medicines optimisation interventions including ensuring that therapy is simplified as much as possible.
- These resources can be found on the PrescQIPP website (don't forget to log in first):
<http://www.prescqipp.info/resources/viewcategory/316-asthma-focus>
<http://www.prescqipp.info/projects/respiratory-care-webkit#inhaler-technique-assessment-tools>

Recommendations

- Ensure all patients have a personalised asthma plan. The Asthma UK/NHS England template plan should be used as the preferred template. <http://www.asthma.org.uk/advice-personal-action-plan>
- Ensure that when a patient is first prescribed an inhaler they are shown how to use it and that they can demonstrate they are able to use it. In children a pressurised metered dose inhaler (pMDI) and spacer or mask is the preferred method of delivery for beta agonists or ICS.
- If more than one inhaler is prescribed, regimens should be kept simple so patients do not have to learn to use many different types of inhaler. For example, if a patient has a pressurised metered dose inhaler (pMDI) reliever and are able to use it (with or without a spacer) then prescribe a pMDI if they need an ICS or ICS/LABA inhaler.
- Ensure inhaler technique is assessed by a healthcare professional on a regular basis. The inhaler [technique assessment support tools](#) can be used by healthcare professionals to support inhaler technique assessment and provide written information to the patient on improving inhaler technique.
- Ensure management of asthma is in line with the BTS/Scottish Intercollegiate Guidelines Network (SIGN) guidelines and patients are regularly reviewed. The pathway documents available on the [PrescQIPP webkit page](#) can be used by healthcare professionals as a guide to where different products fit on the BTS/SIGN guideline for different age groups. Commissioners can also adapt these documents to add local formulary choices.

- Identify and review all patients at high risk of exacerbations and death to ensure their management is improved. Searches and an audit are available to help identify these patients, which include identifying:
 - » Patients who have had more than 12 short acting beta agonists (SABA) in the last 12 months
 - » Patients who have had less than 12 months' worth of ICS inhalers in the last 12 months
 - » Patients taking a LABA alone for asthma, and
 - » Patients who have had more than 2 courses of oral steroids in the last 12 months.
- Ensure patients on high doses of ICS are regularly reviewed and stepping down of treatment is attempted at regular intervals (every three months). [Searches and an audit](#) are available to support this review.

Background

According to Asthma UK¹, about 5.4 million people in the UK have asthma, and the estimated annual cost to the NHS for treating asthma is £1 billion. 180 people a day are admitted to hospital for asthma and worryingly three patients per day, on average, die from asthma.

The recent [National Review of Asthma Deaths](#) (NRAD)² report made some key recommendations about improving the management of asthma, which in some cases has been inadequate. Prescribing data shows there is still a wide variation in numbers of SABA inhalers prescribed and audit often shows that patients do not use regular ICS.

Combination ICS/LABA inhalers are now the most expensive drug class for the NHS. Over £558 million is spent on these drugs nationally over 12 months (ePACT September 2014).

National guidance

The NRAD report was published in May 2014.² This report was based on a review of asthma deaths occurring between February 2012 and January 2013. The primary aim of NRAD was to understand the circumstances surrounding asthma deaths in the UK in order to identify avoidable factors and make recommendations to improve care and reduce the number of deaths. Data was analysed on 195 people who were thought to have died from asthma and the key findings relate to this group. The report found that the majority of people who died from asthma (n=112, 57%) were not recorded as being under specialist supervision during the 12 months prior to death. Only 83 (43%) were managed in secondary or tertiary care during this period; therefore there is significant work that can be done in the primary care setting to improve the care of asthma patients. Many of the recommendations related to prescribing and medicines usage; the key recommendations were:

- Patients using more than 12 SABA inhalers in the past 12 months should be invited for an urgent asthma review with the aim of improving their asthma through education and change of treatment if required.
- An assessment of inhaler technique to ensure effectiveness should be routinely undertaken and formally documented at annual review, and also checked by the pharmacist when a new device is dispensed.
- Non-adherence to preventer ICS is associated with increased risk of poor asthma control and should be continually monitored.
- The use of combination inhalers should be encouraged. Where LABA bronchodilators are prescribed for people with asthma, they should be prescribed with an ICS in a single combination inhaler.

BTS/SIGN³ guidelines on asthma recommend a stepwise approach to asthma treatment. Prescribers are often confused about where a particular product fits on the guidelines and which products to use and/or where to start a patient when they are experiencing an exacerbation of symptoms. Quite often

patients are stepped up but then not regularly reviewed and stepped down the treatment pathway. The asthma pathway tools (<http://www.prescripp.info/resources/viewcategory/316-asthma-focus>) have been developed to support prescribers in identifying where products fit in an asthma pathway. They also contain an adaptable pathway on which local formulary choices can be added.

Before starting a new drug or stepping up treatment, the patients understanding of the role of treatment, adherence to treatment, inhaler technique, and appropriate elimination of trigger factors should be confirmed. Control of asthma should be assessed after an agreed duration, depending on the desired outcome. The guidelines recommend stepping down therapy once asthma is controlled, but this is often not implemented leaving patients over-treated.³ The guidelines suggest that patients should be maintained at the lowest possible dose of inhaled steroid and that reductions be considered every three months, decreasing the dose by approximately 25-50% each time.

It is important to remember that many patients with asthma may be over-treated, and may subsequently be receiving excessive doses of potent ICS and LABA (see Commission on Human Medicines (CHM) advice below). It is therefore recommended that clinicians focus on ensuring that their patients are regularly reviewed. Once asthma control is achieved, the patient's inhaled therapy should be stepped down and when asthma control is not achieved, then therapy should be stepped up appropriately.⁴

Commission on Human Medicines (CHM) advice

Following a trial comparing salmeterol with placebo that reported increased respiratory-related deaths, asthma-related deaths, and combined asthma-related deaths or life threatening experiences in the salmeterol group as compared to the placebo group, the Medicines and Healthcare products Regulatory Agency (MHRA) has advised that for the management of chronic asthma, long acting beta agonists (formoterol and salmeterol) should:^{5,6}

- Be added only if regular use of standard-dose ICS has failed to control asthma adequately.
- Not be initiated in patients with rapidly deteriorating asthma.
- Be introduced at a low dose and the effect properly monitored before considering dose increase.
- Be discontinued in the absence of benefit.
- Be reviewed as clinically appropriate: stepping down therapy should be considered when good long term asthma control has been achieved.
- Be prescribed as combination inhalers when appropriate to aid compliance in line with NICE guidance (see below).

Patients should report any deterioration in symptoms following initiation of treatment with a long-acting beta agonist.

Further advice for use in children

A daily dose of 24 micrograms formoterol should be sufficient for most children, particularly younger age groups. Higher doses should be used rarely, and only when control is not maintained on the lower dose.

LABA should not be prescribed for the relief of exercise-induced asthma symptoms in the absence of regular ICS.

NICE guidance⁷ recommends that for adults, and children aged 12 years and older, with chronic asthma in whom treatment with an ICS and LABA is considered appropriate, the following points apply:

- The use of a combination device within its marketing authorisation is recommended as an option.
- The decision to use a combination device or the two agents in separate devices should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence.
- If a combination device is chosen then the least costly device that is suitable for the individual is recommended.

NICE guidance recommendations for children⁸⁻¹⁰

For children under the age of 12 years with chronic asthma in whom treatment with an ICS and LABA beta agonist is considered appropriate, the following points apply:

- The use of a combination device within its marketing authorisation is recommended as an option.
- The decision to use a combination device or the two agents in separate devices should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence.
- If a combination device is chosen then the least costly device that is suitable for the individual child is recommended.

There is no licenced combination inhaler for use at step 4 of the BTS guidelines for children aged 5 to 12. Commissioners will need to consider the risks vs. benefits of prescribing a combination inhaler for appropriate patients as an off label use, or prescribing separate ICS and LABA inhalers. The use of separate inhalers is not recommended as it could lead to patients using the LABA alone without the ICS which increases the risk of exacerbations and death.²

In addition, for children aged over 5 years a press-and-breathe pressurised metered dose inhaler used with an appropriate spacer is recommended as the first choice of inhaler for use with ICS medicines for asthma (preventers).⁹ If a clinician believes that an individual child will be unlikely to use the press-and-breathe inhaler and spacer properly such that his or her asthma control may be affected, other inhalers should be considered.

For other inhaled medicines for asthma, such as bronchodilators (relievers), a wider range of inhalers should be considered. This recommendation takes into account that the child is more likely to have to carry this inhaler around with him or her so that it is available for use when needed.

The choice of inhaler should be determined by individual needs, including the medicine the child needs, and the child's ability and willingness to use a particular inhaler. If, after these factors have been taken into account, there is more than one inhaler to choose from, the inhaler with the lowest overall cost to the NHS should be chosen.

For children under the age of 5 years who have chronic stable asthma:¹⁰

- Both corticosteroids and bronchodilator therapy should routinely delivered by pressurised Metered Dose Inhaler (pMDI) and spacer system, with a facemask where necessary.
- Where this combination is not clinically effective for the child, and depending on the child's condition, nebulised therapy may be considered and in the case of children aged 3 to 5 years, a dry powder inhaler (DPI) may also be considered.
- The choice of which pMDI device and spacer to use should be determined by the specific needs of the child and how well it works for them. Once these factors have been taken into account the choice should be made on the basis of reducing costs.

The appropriate selection of inhaler devices as described is only one aspect for the provision of a comprehensive approach to all aspects of managing asthma. In particular, parents/carers need education, support and guidance, on how to manage their child's condition. General practitioners, the practice nurse, the specialist asthma nurse, the health visitor and school nurse and other community health carers have an essential role in the provision of this service and advice on general management may result in additional improvements in clinical and cost effectiveness.

High dose inhaled corticosteroids

ICS are safe and effective for the prevention of symptoms of asthma when used regularly at the recommended doses. The BTS/SIGN³ asthma guidelines recommend that regular ICS are prescribed if a patient requires short acting bronchodilator therapy more than twice a week, or if there are night-time symptoms more than once a week, or if there has been an exacerbation in the last two years. Regular use of ICS reduces the risk of exacerbation of asthma. The guidelines also recommend starting ICS at a dose

appropriate to the severity of the disease. Staring at very high doses of ICS in mild to moderate asthma then stepping down confers no benefit.

The adverse event profile of high dose ICS used over a prolonged period are well known. They include adrenal suppression, reduced bone mineral density pre-disposing patients to osteoporosis, diabetes, glaucoma, cataracts, hoarseness, dysphonia, and candidiasis of the mouth or throat. It is therefore sensible to ensure that the dose of an ICS is no higher than necessary to keep a patient's asthma under good control.¹¹ An MHRA review of data for inhaled and intranasal corticosteroids suggests that in addition to the known systemic effects of these medicines, a range of psychological or behavioural effects may also occur. These include psychomotor hyperactivity, sleep disorders, anxiety, depression, and aggression (particularly in children).⁶

The British National Formulary (BNF) advises to:

“Consider giving a ‘steroid card’ to support communication of the risks associated with treatment, and specific written advice to consider corticosteroid replacement during an episode of stress, such as severe intercurrent illness or an operation, to patients using greater than maximum licensed doses of inhaled corticosteroids. Use of other corticosteroid therapy (including topical) or concurrent use of drugs which inhibit corticosteroid metabolism should be taken into account when assessing systemic risk.”¹¹

The London Respiratory Network have developed a high dose ICS safety card for adults, which should be given to any patients aged 12 and over taking high doses of ICS. These additional resources are available here: <http://www.prescqipp.info/resources/viewcategory/316-asthma-focus>

For adults and children aged over 12, high dose ICS are introduced at step four of the BTS/ SIGN guidelines and are defined in the guidelines (given through metered dose inhaler) as:

Greater than or equal to 800 micrograms beclometasone (Clenil Modulite®)
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Greater than or equal to 400 micrograms extra fine beclometasone (Qvar®)
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Greater than or equal to 800 micrograms budesonide
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Greater than or equal to 400 micrograms fluticasone propionate
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Please note: 400 micrograms fluticasone propionate = 80 micrograms fluticasone furoate (dose leaving the mouthpiece).¹²

Spend on high dose ICS nationally is over £299 million (ePACT September 2014). If being used for asthma high dose ICS should be reviewed and a step down attempt made every three months.

Clinical evidence

Drug comparisons in asthma¹³

Inhaled corticosteroids: Fluticasone propionate (FP) vs. beclometasone vs. budesonide

Beclometasone dipropionate (BDP) and budesonide are approximately equivalent in clinical effectiveness, although there may be variations with different delivery devices. There is limited evidence from two open studies of less than ideal design that budesonide via the turbohaler is more clinically effective. However, at present a 1:1 ratio should be assumed when changing between BDP and budesonide. Extra fine BDP and FP provide equal clinical activity to BDP and budesonide at half the dosage. The evidence that fluticasone causes fewer side effects at doses with equal clinical effect is limited.³

Fluticasone Propionate (FP) vs. Fluticasone Furoate (FF)

Although the BTS guidelines express dose equivalences as BDP equivalence, Fluticasone furoate (the steroid in Relvar® Ellipta®) has no BDP equivalence available. The SPC states that:

“Patients with asthma should be given the strength of Relvar® Ellipta® containing the appropriate fluticasone furoate (FF) dosage for the severity of their disease. Prescribers should be aware that in

patients with asthma, fluticasone furoate (FF) 100 micrograms once daily is approximately equivalent to fluticasone propionate (FP) 250 micrograms twice daily, while FF 200 micrograms once daily is approximately equivalent to FP 500 micrograms twice daily.”¹²

Although a direct conversion cannot be made, the following conversions can be applied:

FP 250 micrograms twice a day is approximately equivalent to 1000 micrograms BDP daily

FP 500 micrograms twice a day is approximately equivalent to 2000 micrograms BDP daily³

There are no studies comparing FF to other ICS and it is not available as a single component product.

Long acting beta 2 agonists (LABA): Salmeterol vs. formoterol

The BTS/SIGN guideline on the management of asthma does not name any of the LABAs individually or highlight any differences between them.³ Therefore if one is required, it is up to the prescriber to decide which one to choose.

A Cochrane systematic review examining the safety of regular formoterol or salmeterol in children with asthma concluded that it is not possible to know if regular combination therapy with formoterol or salmeterol in children alters the risk of dying from asthma. Regular combination therapy is likely to be less risky than monotherapy in children with asthma, but it is not possible to say that combination therapy is risk free. There are probably an additional three children per 1000 who suffer a non-fatal serious adverse event on combination therapy in comparison to ICS over three months. This is currently a best estimate of the risk of using LABA combination therapy in children and has to be balanced against the symptomatic benefit obtained for each child. The results of large on-going surveillance studies to further clarify the risks of combination therapy in children and adolescents with asthma are awaited. The relative safety of formoterol in comparison to salmeterol remains unclear, even when all currently available direct and indirect trial evidence is combined.¹⁴

Vilanterol is a LABA drug which is only available in a combination product.

Comparison between the ICS/LABA combination products

Table 1 shows the different ICS/LABA combination products available and whether they have been compared head to head in clinical trials.

Table 1: Published head to head, clinical, comparative studies of the combination inhalers

Product	Published studies in asthma	
Flutiform® vs Fostair®	X	
Flutiform® vs Relvar®	X	
Flutiform® vs Seretide®	✓	Flutiform® non-inferior to Seretide® ¹⁵
Flutiform® vs Symbicort®	✓	Flutiform® non-inferior to Symbicort® ¹⁷
Fostair® vs Relvar®	X	
Fostair® vs Seretide®	✓	Fostair® has similar efficacy to Seretide® ¹⁹
Fostair® vs Symbicort®	✓	Fostair® has similar efficacy to Symbicort® ²⁰
Seretide® vs Symbicort®	✓	Clinical equivalence assumed by NICE ^{7,21-25}
Relvar® vs Seretide®	✓	Relvar® has similar efficacy to Seretide® ²⁶
Relvar® vs Symbicort®	X	

Flutiform®

The efficacy of fluticasone/formoterol 50/5 micrograms or 125/5 micrograms, two actuations twice daily (Flutiform®) was compared with fixed dose fluticasone/salmeterol 50/25 micrograms or 125/5 micrograms, two actuations twice daily (Seretide® pMDI) in an open label, parallel group, 12 week randomised study in 202 adults (189 completed) with mild to moderate to severe persistent asthma. Flutiform® was shown to be non-inferior to Seretide® in the primary outcome of pre-dose FEV1 at week 12. Non-inferiority of Flutiform® relative to Seretide® was demonstrated as LS mean pre-dose FEV1

treatment difference from baseline to the end of week 12 (-0.061L; 95% CI: -0.161, 0.040; P=0.007). A secondary outcome showed that Flutiform® had a more rapid onset of action than Seretide®.^{15,16}

A double-blind, double-dummy, randomised, parallel group, multicentre 12 week study in 279 adults and adolescents (261 completed) with moderate to severe persistent asthma was carried out to demonstrate non-inferiority of fluticasone/formoterol (Flutiform®) 125/5 micrograms, two actuations twice daily, (n=140) relative to budesonide/formoterol (Symbicort®) 200/6 micrograms, two actuations twice daily, (n=139). The primary endpoint was difference in FEV1 from baseline to end of week 12. Non-inferiority of Flutiform® relative to Symbicort® was demonstrated as least squares (LS) mean pre-dose FEV1 treatment difference from baseline to the end of week 12 (-0.044 L; 95% CI: -0.130, 0.043; P<0.001). Flutiform® also had a similar tolerability profile to Symbicort. 29 patients (20.7%) in the Flutiform® group and 26 (18.7%) in the Symbicort® group reported at least one adverse event (AE). The majority of AEs were mild or moderate in intensity.¹⁷

The SMC has also reviewed Flutiform®¹⁸ and state:

“Flutiform® should be used in patients for whom fluticasone and formoterol are appropriate choices of corticosteroid and long-acting beta-agonist, respectively, and for whom a metered dose inhaler is an appropriate delivery device. It has demonstrated clinical non-inferiority to another combination product containing a corticosteroid and long-acting beta2-agonist and may offer cost savings.”

Fostair®

Fostair® 100/6 inhaler has been compared with a number of other inhaler devices in order to gain marketing authorisation from the MHRA, who only require the manufacturer to submit and prove non-inferiority when compared with a brand currently available on the UK market. The first was a randomised double blind phase III study by Papi et al who compared Fostair® 100/6 inhaler with Seretide®125 Evohaler in 228 patients with moderate to severe asthma symptoms.¹⁹ The dose ratio of beclometasone: fluticasone was 1:1.25, which is different from the traditional equivalence reported in the equivalence table of ICS in several international guidelines. The main outcome of the study was morning peak expiratory flow (PEF). The authors were able to show non inferiority to the marketed Seretide®125 Evohaler in terms of efficacy and tolerability. However, the study did highlight that use with Fostair® 100/6 inhaler was associated with a significantly faster onset of bronchodilation when compared with Seretide®125 Evohaler. The overall rate of asthma exacerbations and frequency of adverse effects were no different between the two groups.

A second randomised, double-blind, parallel group, 3 months, phase III study also by Papi et al compared Fostair® 100/6 inhaler with Symbicort®200 Turbohaler in 219 patients with moderate to severe asthma symptoms.²⁰ The dose ratio of beclometasone: budesonide was 1:2, which is different from the traditional equivalence reported in the equivalence table of ICS in several international guidelines. The authors were again able to show non inferiority to the marketed Symbicort®200 Turbohaler in terms of efficacy and tolerability. This trial was also able to demonstrate that there was no difference observed between the two groups in either rate of asthma exacerbations and frequency of adverse effects.

Seretide® and Symbicort®

The NICE TA on use of corticosteroids for asthma in adults and children aged 12 years and over⁷ highlighted three RCTs which have evaluated the effectiveness of Symbicort® (budesonide/formoterol fumarate) (approximately 800 micrograms budesonide, 24 micrograms formoterol fumarate using the Turbohaler device) with Seretide® (fluticasone propionate/salmeterol) (approximately 500 micrograms fluticasone propionate, 100 micrograms salmeterol using the Accuhaler® device).²³⁻²⁵ Results of these studies were mixed. Some studies reported statistically significant improvements for some outcomes with Symbicort® while others reported statistically significant improvements with Seretide®. One RCT reported significant improvements in lung function with the Symbicort® inhaler, and two RCTs reported significant improvements in lung function with the Seretide® inhaler. Two RCTs reported a significant reduction in the rate of exacerbations with the Symbicort® inhaler, and one RCT reported a significant

reduction in the rate of exacerbations with the Seretide® inhaler. The use of rescue medication was significantly lower with Seretide® in one RCT. There were no differences between the Symbicort® and the Seretide® inhalers in two RCTs which reported on asthma symptoms, health related quality of life, or the rate of adverse events. A third RCT reported a significant reduction in symptom-free days with Seretide®. The NICE TA surmised that clinical equivalence of the two combination inhalers was assumed. A Cochrane review comparing Seretide® and Symbicort® concluded that neither therapy was superior due to statistical imprecision in the effect estimates for exacerbations and serious adverse events in the trials.^{7,21,22}

Relvar® Ellipta®

Relvar® Ellipta® is a new combination ICS/LABA that contains fluticasone furoate and vilanterol. There is only one study comparing the efficacy of Relvar® Ellipta® with another ICS/LABA combination product (Seretide). This was a superiority study with the hypothesis that Relvar 92/22mcg OD would demonstrate superior efficacy over Seretide®250/50mcg BD. No statistically significant difference was found between fluticasone furoate/vilanterol 92/22 micrograms once daily and fluticasone propionate/salmeterol 250/50 micrograms twice daily for the 0-24 hour weighted mean forced expired volume in 1 second (FEV₁) week-24 change from baseline. Because statistical significance was not achieved for the primary endpoint, statistical significance cannot be inferred for comparisons of secondary endpoints.^{26,27}

DuoResp Spiromax®

DuoResp Spiromax® is a new dry powder inhaler containing budesonide and formoterol which has been granted a license based on its equivalence to Symbicort® Turbohaler via an EU hybrid license application.²⁸ Three strengths of DuoResp Spiromax® were initially proposed: budesonide 80 µg and formoterol (as fumarate dihydrate) 4.5 µg, budesonide 160 µg and formoterol (as fumarate dihydrate) 4.5 µg and budesonide 320 µg and formoterol (as fumarate dihydrate) 9 µg. During the process, the lowest strength was withdrawn since neither in vitro equivalence, nor bioequivalence with Symbicort Turbohaler was demonstrated (note doses are expressed as delivered dose rather than metered dose). Studies in patients have to date been limited to tests to determine that DuoResp Spiromax® is bioequivalent to the reference medicine, Symbicort® Turbohaler.

Safety

A Cochrane²⁹ review looking at the safety of formoterol plus ICS and salmeterol plus ICS looked at seven studies in adults and concluded these did not show any significant difference in safety between formoterol and budesonide in comparison with salmeterol and fluticasone. Asthma-related serious adverse events were rare, and there were no reported asthma-related deaths. There was also a single small study comparing formoterol and beclometasone to salmeterol and fluticasone in adults, but no serious adverse events occurred in this study. No studies were found looking at the safety of ICS/LABA combinations in children.

The authors concluded that overall there is insufficient evidence to decide whether regular formoterol and budesonide or beclometasone have equivalent or different safety profiles from salmeterol and fluticasone.

For Relvar® Ellipta®, as discussed above, fluticasone furoate is approximately five times the potency of fluticasone propionate. There are also however conflicting statements in the SPC of Relvar® Ellipta® which states the 92/22 dose is low to mid dose and the 184/22 is considered to be the higher dose^{12,30} This directly conflicts the statements in the SPCs which provide the equivalence to fluticasone propionate which could place both doses as high dose on the BTS guidelines. There have also been concerns raised about the limited ability for stepping down treatment with this product.²⁷

A UKMI in use product safety assessment of Relvar® Ellipta®³¹ discussed concerns that were raised about the product since its launch, which included:

- The potential for confusion on whether the product is a reliever or preventer inhaler- the name Relvar sounds like reliever and the packaging is blue which is usually associated with reliever inhalers.
- There are confusing aspects to the labelling such as the use of the conventional mcg for micrograms as well as the unconventional µg and the use of three different languages on the packaging.
- Once opened the product has a six week expiry date which could lead to patients accidentally using expired inhalers.

On 20th October 2014, GSK submitted for a Type IA licence variation for Relvar® Ellipta®, which has been accepted by the European Medicines Agency (EMA).³²

The changes include the following updates:

- Changing the colour of the inhaler mouthpiece cover, packaging and associated labelling from pale blue to yellow.
- Addition of new colour indicators to provide differentiation between the two product strengths of Relvar® Ellipta®.
- Including the patient in-use shelf-life for opened product.
- Revising the text to clarify patient instructions.

These changes will come into effect at the end of January 2015.³²

Relvar® Ellipta® and Flutiform® are black triangle drugs and therefore subject to intensive monitoring by the MHRA.¹¹

LAMA inhalers

Tiotropium (Spiriva Respimat®) received a licence extension to treat asthma in adults in September 2014.³³ The licence states:

“Spiriva Respimat is indicated as an add-on maintenance bronchodilator treatment in adult patients with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (≥800 mcg budesonide/day or equivalent) and long-acting beta2 agonists and who experienced one or more severe exacerbations in the previous year.”

The BTS/SIGN asthma guideline (updated October 2014) states:³

“Long-acting muscarinic antagonists appear to be as effective as salmeterol in the short term and may be superior to doubling the dose of ICS in fixed airways obstruction. Longer term studies are required to confirm this evidence. There would also appear to be benefit in adding tiotropium to ICS and salmeterol in patients who remain symptomatic despite these medications.”

This statement is under the recommendations for add on treatments for consideration at step 4 although LAMA's have not yet been placed on the treatment pathway on the BTS/SIGN guidelines for asthma.

Costs

Focus should be on reviewing patients on ICS and LABAs and stepping down their treatment (where appropriate) to ICS alone, rather than solely focusing on switching to a cheaper combination inhaler. Better management with regular clinical review and stepping down as appropriate may provide greater cost-savings and better quality care. Where more than one product is suitable and acceptable to the individual, then the least costly should be chosen. The tables below show cost comparisons of the ICS/LABA inhalers at different treatment levels. The [PrescQIPP pathway documents](#) have full costings for treatments at each step of the BTS pathway for adults and children.

Table 2: Low dose ICS/LABA combination inhaler product and price comparison^{11, 34}

Product	ICS/LABA quantity per puff	Beclometasone (BDP) equivalent daily dose	Dose	Type of inhaler device	Cost for 30 days
Fostair® 100/6 Inhaler	Beclometasone 100 micrograms (equivalent to 250 micrograms BDP non extra fine)/formoterol 6 micrograms	500 micrograms	1 puff twice daily	MDI	£14.66
Fostair 100/6 NEXThaler®	Beclometasone 100 micrograms (equivalent to 250 micrograms BDP non extra fine)/formoterol 6 micrograms	500 micrograms	1 puff twice daily	Breath actuated dry powder inhaler	£14.66
DuoResp Spiromax® 160/4.5 inhaler	Budesonide 200 micrograms/formoterol 6 micrograms (expressed as delivered dose on strength)	400 micrograms	1 puff twice daily	Breath actuated dry powder inhaler	£14.99
Flutiform® 50/5 inhaler	Fluticasone 50 micrograms/formoterol 5 micrograms	400 micrograms	2 puffs twice daily	MDI	£18.00
Seretide® 50 Evohaler	Fluticasone 50 micrograms/salmeterol 25 micrograms	400 micrograms	2 puffs twice daily	MDI	£18.00
Seretide® 100 Accuhaler	Fluticasone 100 micrograms/salmeterol 50 micrograms	400 micrograms	1 puff twice daily	Breath-actuated	£18.00
Symbicort® 200/6 Turbohaler	Budesonide 200 micrograms/formoterol 6 micrograms	400 micrograms	1 puff twice daily	Breath-actuated dry powder	£19.00
Symbicort® 100/6 Turbohaler	Budesonide 100 micrograms/formoterol 6 micrograms	400 micrograms	2 puffs twice daily	Breath-actuated dry powder	£33.00

Moderate dose ICS/LABA combination inhaler product and price comparison^{11, 34}

Product	ICS/LABA quantity per puff	BDP equivalent daily dose	Dose	Type of inhaler device	Cost for 30 days
DuoResp Spiromax® 160/4.5 inhaler	Budesonide 200 micrograms/formoterol 6 micrograms (expressed as delivered dose in product strength)	800 micrograms	2 puffs twice daily	Breath actuated dry powder inhaler	£29.97
DuoResp Spiromax® 320/9 inhaler	Budesonide 400 micrograms/formoterol 12 micrograms (expressed as delivered dose in product strength)	800 micrograms	1 puff twice daily	Breath actuated dry powder inhaler	£29.97
Symbicort® 200/6 Turbohaler	Budesonide 200 micrograms/formoterol 6 micrograms	800 micrograms	2 puffs twice daily	Breath actuated dry powder	£38.00
Symbicort® 400/12 Turbohaler	Budesonide 400 micrograms/formoterol 12 micrograms	800 micrograms	1 puff twice daily	Breath actuated dry powder	£38.00

High dose ICS/LABA combination inhaler product and price comparison (high dose is over 800 micrograms BDP equivalent)^{11, 34}

Product	ICS/LABA quantity per puff	Beclometasone (BDP) equivalent daily dose	Dose	Type of inhaler device	Cost for 30 days
Greater than 800 microgram and up to 1000 microgram BDP equivalent					
Flutiform® 125/5 inhaler	Fluticasone 125 micrograms/formoterol 5 micrograms	1000 micrograms	2 puffs twice daily	MDI	£29.26
Fostair® 100/6 Inhaler	Beclometasone 100 micrograms (equivalent to 250 micrograms BDP non extra fine)/formoterol 6 micrograms	1000 micrograms	2 puffs twice daily	MDI	£29.32
Fostair 100/6 NEXThaler®	Beclometasone 100 micrograms (equivalent to 250 micrograms BDP non extra fine)/formoterol 6 micrograms	1000 micrograms	2 puffs twice daily	Breath actuated dry powder inhaler	£29.32
Seretide®125 Evohaler	Fluticasone 125 micrograms/salmeterol 25 micrograms	1000 micrograms	2 puffs twice daily	MDI	£35.00
Seretide® 250 Accuhaler	Fluticasone 250 micrograms/salmeterol 50 micrograms	1000 micrograms	1 puff twice daily	Breath actuated	£35.00
1000 to 2000 microgram BDP equivalent					
Flutiform® 250/5 inhaler	Fluticasone 250 micrograms/formoterol 5 micrograms	2000 micrograms	2 puffs twice daily	MDI	£45.56
Seretide® 500 Accuhaler	Fluticasone 500 micrograms/salmeterol 50 micrograms	2000 micrograms	1 puff twice daily	Breath actuated	£40.92
Seretide® 250 Evohaler	Fluticasone 250 micrograms/salmeterol 25 micrograms	2000 micrograms	2 puffs twice daily	MDI	£59.48
DuoResp Spiromax® 320/9 inhaler	Budesonide 400 micrograms/formoterol 12 micrograms (expressed as delivered dose in product strength)	1600 micrograms	2 puff twice daily	Breath actuated dry powder inhaler	£59.94
Symbicort® 400/12 Turbohaler	Budesonide 400 micrograms/formoterol 12 micrograms	1600 micrograms	2 puffs twice daily	Breath actuated dry powder	£76.00

BTS/SIGN did not review the evidence for Relvar® Ellipta® in the 2014 update of their asthma guidelines³ and this product is difficult to fit into the asthma treatment pathway due to the conflicting statements on the SPC and the lack of a comparable BDP equivalent dose. Because fluticasone furoate is a new ICS, more information about its effect on cortisol suppression relative to other ICS is needed. The product and price comparisons for Relvar® Ellipta® are shown below.

Relvar® Ellipta® product and price comparison^{11, 34}

Product	ICS/LABA quantity per puff	Alternative steroid inhaler equivalent daily dose	Dose	Type of inhaler device	Cost for 30 days
Relvar® Ellipta® 92/22 inhaler	Fluticasone furoate 92 micrograms vilanterol 22 micrograms expressed as delivered dose	Equivalent to 500micrograms FP	1 puff daily	Breath actuated dry powder inhaler	£27.80
Relvar® Ellipta® 184/22 inhaler	Fluticasone furoate 184 micrograms vilanterol 22 micrograms expressed as delivered dose	Equivalent to 1000micrograms FP	1 puff daily	Breath actuated dry powder inhaler	£38.87

Options for treatment review and switching

NICE guidance states that if a combination steroid inhaler device is required, then the least costly device that is suitable for the individual is recommended.⁷ When making a formulary choice consideration should be given to ability to step down and also minimising range of inhaler types the patient needs to use.

For low dose and moderately high dose ICS/LABA combination inhalers Fostair® remains a cost-effective choice, however Flutiform® does offer a cost effective option across the range for low, medium (moderately high) and high dose ICS/LABA combination and is also an option to switch from fluticasone containing combination products if clinicians do not wish to change the steroid the patient is receiving. It is worth noting that Fostair®, Flutiform®, Relvar® Ellipta® and Seretide® do not fit exactly to BTS treatment pathway as the middle dose for these products would relate to 1000mcg BDP equivalent (500 mcg FP for Relvar® Ellipta®).

There are potentially £8.9 million worth of savings to be made across England by stepping patients down to low or moderate treatment doses of ICS/LABA inhalers. **This equates to £15,777 per 100,000 patients.** NB. In reality the full effect of these savings may not be reached as some of the spend may be for COPD treatment.

Switching patients to low or moderate dose least costly inhalers (Fostair®, Flutiform® and DuoResp Spiromax®) **could save up to £3.8 million in England** annually, (based on upper quartile prescribing). **This equates to £6,631 per 100,000 patients.**

DuoResp Spiromax® has been granted a license as equivalent to Symbicort® via an EU hybrid license application. Switching Symbicort® (200/6 and 400/12 inhalers only) on a dose for dose basis could release 20% savings **which equates to £14.6 million annually across England or £25,858 per 100,000 patients.**

The attached data pack also shows variation in practice for reliever inhalers, peak flow meters, spacer devices for adults and children, montelukast and short courses of prednisolone. This data has been added to the data packs to support CCGs in reviewing their asthma and respiratory prescribing. The savings figures above are not cumulative.

Summary

- Although there are savings to be made by switching asthma treatments, focus should be on stepping down patients to the lowest effective dose of ICS and ensuring that asthma is well controlled and appropriately managed. Reviewing the patients who have the trigger factors identified in the NRAD report and ensuring their therapy is optimised will result in fewer hospital admissions and deaths from asthma.

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Additional PrescQIPP resources



Briefing



Data pack



Patient information leaflets, audit,
system searches, guidance

Available here: <http://www.prescqipp.info/resources/viewcategory/316-asthma-focus>

Inhaler technique assesment tools:

<http://www.prescqipp.info/projects/respiratory-care-webkit#inhaler-technique-assessment-tools>

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