

Adding a long-acting beta₂-agonist (LABA) to asthma treatment for adults

If a patient using an inhaled corticosteroid for asthma has symptoms which are not adequately controlled, clinicians should consider adding a LABA to their regimen in the form of a combined ICS/LABA inhaler. Use of an ICS/LABA inhaler as both reliever and preventer treatment is preferred for patients at high risk of exacerbation, known as single inhaler treatment.

KEY PRACTICE POINTS:

- The four-stage consultation framework for managing patients with asthma in primary care recommends that pharmacological treatment is regularly reviewed, and if necessary adjusted, according to the patient's symptoms and risk of exacerbations (Stage three of the consultation)
- If patients have inadequately controlled asthma symptoms while using a standard dose ICS inhaler, add a LABA to their treatment regimen rather than increasing the ICS dose
- Prescribe a combination ICS/LABA inhaler, rather than separate ICS and LABA inhalers
- Patients should initiate a combination ICS/LABA inhaler with a dose of ICS equivalent to the dose they were using with their ICS inhaler
- Single inhaler treatment (also known as SMART) is recommended for patients at risk of severe exacerbations

The New Zealand Adult Asthma Guidelines recommend a stepwise treatment model for the pharmacological management of asthma. Adult patients with asthma who have

been prescribed an inhaled corticosteroid (ICS) preventer (Step 2), but still have poorly or partly controlled symptoms, may require the addition of a long-acting beta₂-agonist (LABA) to their treatment regimen, either at Step 3 or 4 (Figure 1).

Use the four-stage asthma consultation process

Adjustments to treatment based on the patient's control of symptoms and risk of exacerbations are recommended at Stage three of the four-stage asthma consultation plan presented in the New Zealand Adult Asthma Guidelines.¹ An escalation of treatment from an ICS preventer should only be done after assessing asthma control (Stage one of the consultation) and considering whether other clinical issues or treatable traits are contributing to a patient's symptoms (Stage two). After adjusting treatment, the patient's asthma action plan should be updated (Stage four).

 For further information, see: "Managing adults with asthma in primary care: the four-stage consultation", www.bpac.org.nz/2017/asthma.aspx

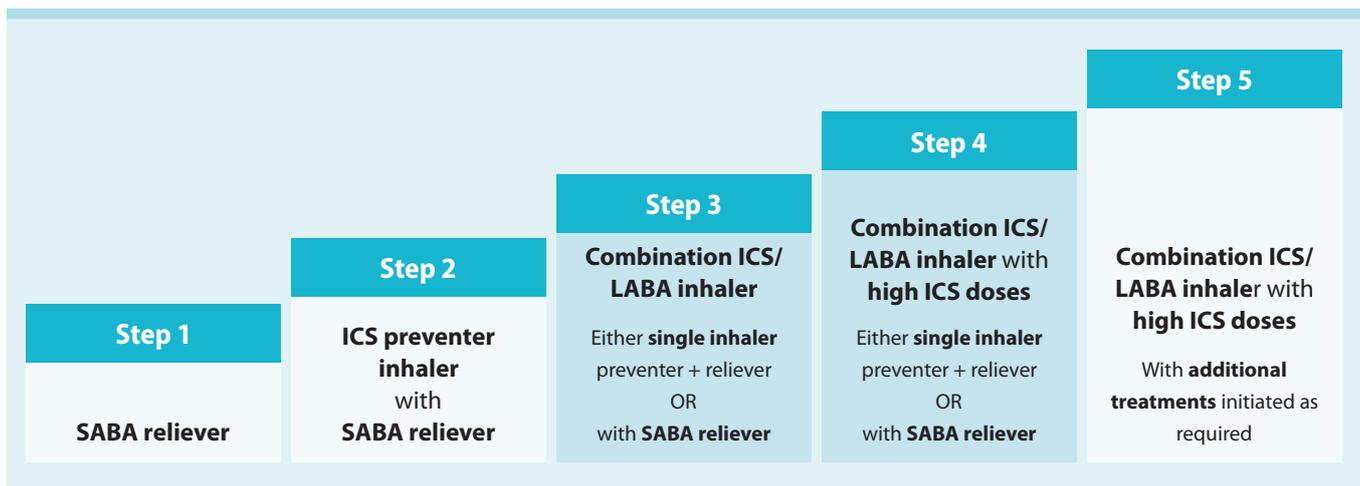


Figure 1: Patients with asthma inadequately controlled with an ICS preventer inhaler (Step 2) may require the use of a combination ICS/LABA inhaler (Steps 3 and 4). Adapted from Beasley *et al*, 2016.¹

Escalating treatment from an ICS preventer inhaler to an ICS/LABA inhaler

A patient with asthma using an ICS at the recommended standard dose will receive 80 – 90% of the maximum obtainable benefit of an ICS.^{2,3} Therefore, if patients require a step-up of treatment they should have a LABA added to their regimen rather than increasing the ICS dose.^{1,4,5} Regular use of a LABA provides long-acting bronchodilation and results in improved lung function, reduced symptoms and a reduced risk of exacerbations.⁴

Prescribe a combination ICS/LABA inhaler

A LABA should be added to treatment by prescribing a combination ICS/LABA inhaler and discontinuing the previously used ICS inhaler. Patients who are prescribed separate ICS and LABA inhalers could potentially have poor adherence to their ICS inhaler and in effect be using LABA monotherapy. LABA monotherapy is associated with a small but significant increase in the risk of asthma-related mortality, and therefore this practice is not recommended.⁶ Combination ICS/LABA inhalers can be prescribed fully subsidised without patients needing to first trial separate ICS and LABA inhalers.

N.B. Combination inhalers containing ICS and long-acting muscarinic agonists (LAMAs) are not indicated or recommended for the treatment of asthma.

Maintain an equivalent dose of ICS when starting patients on an ICS/LABA inhaler

When patients are stepped up from an ICS preventer inhaler to an ICS/LABA inhaler, their dose of ICS should remain the same (or equivalent if a different ICS is used).¹ Therefore:

- Patients using a standard daily dose of an ICS preventer inhaler can initially be prescribed any ICS/LABA inhaler at the doses shown in Step 3 of the New Zealand Adult

Asthma Guidelines pharmacological treatment model (Tables 1 and 2)

- Patients using high doses of an ICS preventer inhaler can be commenced at Step 4 (Tables 1 and 2)

Patients can be switched from any of the subsidised ICS preventer inhalers to any of the subsidised combination ICS/LABA inhalers, and do not necessarily need to continue on the same ICS.

For further information on clinically equivalent standard doses of ICS, see: “Inhaled corticosteroids for adults with asthma”, www.bpac.org.nz/2017/ics.aspx

Choosing a reliever treatment: SABA or single inhaler treatment?

When patients are escalated to a combination ICS/LABA inhaler, a key clinical decision is whether they continue to use their short-acting beta₂-agonist (SABA) reliever, or whether they use an ICS/LABA inhaler as both a preventer and reliever, without SABA use; referred to as single inhaler treatment or SMART (Single inhaler Maintenance And Reliever Therapy).

See: “Clarifying the use of acronyms” for further information on the use of single inhaler or SMART terminology in this series of articles.

Single inhaler treatment is recommended for patients at high risk of severe exacerbations (see: “Risk factors for asthma exacerbations”, Page 5).^{1,4} For other patients, either a single inhaler treatment or ICS/LABA + SABA regimen can be used, and the choice may depend on the patient’s preference of inhaler devices (Tables 1 and 2).⁷

The use of single inhaler treatment may allow patients to self-titrate their ICS dose to achieve the best symptom control. This regimen may also be particularly useful for patients with

Table 1: Subsidised inhaler options for adding a LABA to an ICS as single inhaler treatment.^{1,7}

Active ingredients	Dose per inhalation	Patients should take		Subsidised inhaler brand and type
		As daily preventer treatment	As reliever when necessary	
Initial doses – Step 3 of the New Zealand Adult Asthma Guidelines				
Budesonide + formoterol	100 micrograms + 6 micrograms	Two inhalations, twice daily	One inhalation *	Symbicort DPI †
	200 micrograms + 6 micrograms	One inhalation, twice daily	One inhalation *	Symbicort DPI †
Higher doses – Step 4 or 5 of the New Zealand Adult Asthma Guidelines				
Budesonide + formoterol **	200 micrograms + 6 micrograms	Two inhalations, twice daily	One inhalation *	Symbicort DPI †

† Symbicort is the only brand of inhaler registered by Medsafe for use as single inhaler treatment

* Additional inhalations can be taken, one at a time, if symptoms persist after a few minutes. Patients should take no more than six inhalations for relief of acute symptoms.¹³

** Budesonide + formoterol, 400 micrograms + 12 micrograms, is not recommended for patients with asthma

Table 2: Subsidised treatment options for adding a LABA to an ICS, with ongoing use of a SABA reliever inhaler.⁷

ICS + LABA as preventer inhaler				SABA reliever inhaler	
Active ingredients	Dose per inhalation	Patients should take	Subsidised inhaler brand and type		
Initial doses – Step 3 of the New Zealand Adult Asthma Guidelines					
Fluticasone propionate + salmeterol	50 micrograms + 25 micrograms	Two inhalations, twice daily	RexAir MDI Seretide MDI	One or two inhalations of a SABA inhaler, as necessary	
	100 micrograms + 50 micrograms	One inhalation, twice daily *	Seretide DPI		
Budesonide + formoterol	100 micrograms + 6 micrograms	Two inhalations, twice daily	Vannair MDI Symbicort DPI		
	200 micrograms + 6 micrograms	One inhalation, twice daily	Vannair MDI Symbicort DPI		
Higher doses – Step 4 or 5 of the New Zealand Adult Asthma Guidelines					
Fluticasone propionate + salmeterol	125 micrograms + 25 micrograms	Two inhalations, twice daily	RexAir MDI Seretide MDI		One or two inhalations of a SABA inhaler, as necessary
	250 micrograms + 50 micrograms †	One inhalation, twice daily *	Seretide DPI		
Budesonide + formoterol **	200 micrograms + 6 micrograms	Two inhalations, twice daily	Vannair MDI Symbicort DPI		
	Fluticasone furoate + vilanterol	100 micrograms + 25 micrograms	One inhalation, once daily	Breo Ellipta DPI	

MDI = Metered Dose Inhaler. The use of a spacer is recommended with a metered dose inhaler.¹ DPI = Dry Powder Inhaler

* No more than two doses per day⁷

** Budesonide + formoterol, 400 micrograms + 12 micrograms, is not recommended for patients with asthma

† Fluticasone propionate 250 micrograms + salmeterol 25 micrograms in a metered dose inhaler is not subsidised

poor adherence to their ICS preventer treatment, since they will be receiving ICS when they use their inhaler for relief of acute symptoms.⁸

Single inhaler treatment can reduce the risk of exacerbations

A reliever inhaler requires a rapid onset of action to be effective; patients with asthma are initially prescribed a SABA (e.g. salbutamol) to provide quick relief of acute symptoms. Formoterol is a LABA with a rapid onset of action, and it can be used as a reliever medicine, in addition to its use as a preventer medicine. A combination ICS/LABA inhaler containing formoterol produces a 15% improvement in forced expiratory volume over one second (FEV₁) within five to ten minutes, which is similar to that observed with salbutamol.⁹

Using an ICS/formoterol inhaler as both a preventer and reliever has been shown to reduce the risk of severe exacerbations in patients at risk. Randomised controlled trials in patients who had at least one exacerbation in the previous year, and who were taking regular high dose ICS preventer treatment and in need of regular use of a SABA reliever inhaler, found that initiating budesonide + formoterol as single inhaler treatment reduced the risk of severe exacerbations and resulted in less use of oral corticosteroids during exacerbations, than initiating an ICS/LABA inhaler as a preventer with a SABA reliever inhaler.¹⁰

Symbicort (budesonide + formoterol) is used in a single inhaler treatment regimen

There are two fully subsidised brands of inhalers containing budesonide + formoterol: Symbicort (dry powder inhaler) and Vannair (metered dose inhaler). Both devices have proven efficacy in reducing severe exacerbations; however, currently only Symbicort is registered by Medsafe for use as single inhaler treatment.¹

Vilanterol is another LABA with a quick onset of action, however, ICS/LABA inhalers containing vilanterol have not

been studied as single inhaler treatment and are not indicated for this use.¹¹ Combination ICS/LABA inhalers containing salmeterol cannot be used as a reliever inhaler as salmeterol has a slow onset of action.

Key prescribing points for single inhaler treatment or LABA/ICS + SABA regimens

For initiating a patient on single inhaler treatment:¹

- Symbicort is the only brand of inhaler currently registered for use as single inhaler treatment
- Patients should not be prescribed a SABA inhaler
- Emphasise to patients the change in approach to acute symptom relief:
 - Patients will be familiar with using an ICS preventer and SABA reliever inhaler. A change to one inhaler for both uses will be a new concept.
 - Patients will already have a SABA reliever, and possibly additional repeats of SABA inhalers from previous prescriptions. Advise patients not to use or collect these inhalers and only use the combination ICS/LABA inhaler for symptom relief.
- When used as a reliever, patients should only take **one inhalation at a time**, unlike SABA relievers where two inhalations may be used. If symptoms persist an additional inhalation can be taken.
- Patients should be advised to contact their general practice if they are using their inhaler as a reliever more than six times per day

For initiating a patient on an ICS/LABA inhaler with SABA reliever:¹

- Emphasise to patients that they should discontinue using their previous ICS inhaler, not collect any remaining repeats of ICS inhaler prescriptions, and instead use the newly prescribed ICS/LABA inhaler
- Patients should continue with the same approach to reliever treatment

Clarifying the use of acronyms

Many clinicians will be familiar with the term “SMART” in relation to asthma treatment; however this term has various meanings in clinical practice and research.

SMART is used as an abbreviation for Single inhaler Maintenance And Reliever Therapy, which is also sometimes referred to as Symbicort Maintenance And Reliever Therapy or Maintenance And Reliever Therapy (MART).¹² The SMART trial was an important clinical trial in the field of asthma management which compared salmeterol or placebo treatment for patients with asthma

(i.e. it did not study single inhaler treatment). In the future, inhalers that incorporate technology, such as audio reminders of missed doses and synchronisation with computer or phone software, are likely to become commonplace in asthma treatment. These devices are known as Smart Inhalers, which does not refer to single inhaler treatment.

Given the diverse use of the term “Smart” in asthma, the phrase “single inhaler treatment” is used in this article to describe using an ICS/LABA inhaler as both preventer and reliever treatment, to avoid any confusion.

- Patients should be advised to contact their general practice if they are using their reliever inhaler more than six times per day

Managing any adverse effects of ICS/LABA treatment

The most common adverse effects in patients using ICS/LABA inhalers in clinical trials are headache, nasopharyngitis, sinusitis and upper respiratory tract infections, which occur in up to 10% of patients; however, these are no more common than in patients taking ICS alone.^{14, 15} Patients may also experience fine tremor of the hands, muscle cramps or palpitations with LABA use.⁷

LABAs cause an increase in blood glucose levels of approximately 1 mmol/L within two to three hours of administration, and may influence blood glucose management in patients with diabetes.^{7, 16} Using a LABA may increase the risk of hypokalaemia, particularly in patients who are already predisposed, e.g. taking other medicines which also reduce serum potassium such as thiazide and loop diuretics, oral or injectable hydrocortisone or theophylline.^{7, 13}

In patients using ICS/LABA inhalers who have well controlled asthma symptoms for three months or more and are at low risk of exacerbations, stepping down treatment is an option which can reduce the risk of adverse effects.¹

 For further information on adverse effects, contraindications and cautions for LABAs, see the NZF: www.nzf.org.nz/nzf_1705

Provide patients with an appropriate asthma action plan

All patients with asthma should be provided with an asthma plan corresponding to their prescribed medicines and agreed approach to managing their symptoms (Stage four of the asthma consultation). This plan should be updated whenever the patient's treatment regimen is altered:

- For patients initiating single inhaler treatment, provide them with a completed action plan (referred to as SMART in this plan): www.nzasthmaguidelines.co.nz/uploads/8/3/0/1/83014052/smart_asthma_action_plan.pdf
- For patients initiating an ICS/LABA inhaler with SABA reliever provide them with a completed three stage Asthma Action Plan: www.nzasthmaguidelines.co.nz/uploads/8/3/0/1/83014052/3_stage_asthma_action_plan.pdf

 For further information on Asthma Action Plans, see: "Managing adults with asthma in primary care: the four-stage consultation", www.bpac.org.nz/2017/asthma.aspx

Follow up of patients prescribed an ICS/LABA inhaler

The duration of treatment required for a patient's asthma control to improve after adding a LABA can depend on the characteristics of their asthma and the reasons for escalating treatment. Patients with frequent nocturnal awakenings may

Risk factors for asthma exacerbations.

Adapted from Beasley *et al.**

Features related to asthma:

- Poor symptom control, e.g. an Asthma Control Test Score* of ≤ 15
- Hospitalisation or emergency department visit in the last year, or ever having been admitted to intensive care or intubated for treatment of an asthma attack
- SABA use of > 1 canister per month
- Underuse or poor adherence to ICS treatment
- The use of a home nebuliser
- History of sudden asthma attacks
- $FEV_1 < 60\%$ predicted
- Raised blood eosinophil count
- The need for long-term or repeated courses of oral corticosteroids
- Occupational asthma

Co-morbidities:

- Smoking
- Misuse of alcohol or drugs
- Use of psychotropic medicines
- Sensitivity to aspirin or non-steroidal anti-inflammatory medicines

Other factors:

- Māori or Pacific ethnicity
- Socioeconomic disadvantage
- Discontinuity of medical care
- Major psychosocial problems

* The Asthma Control Test comprises five questions and can be conducted with the patient to assess their level of symptom control. Each question is scored from 1 – 5, with higher scores indicating good control: www.asthmacontrol.co.nz

improve within days to weeks, whereas it may take six weeks or more for good control to be established in patients using oral corticosteroids after a severe asthma attack who have not previously used an ICS/LABA inhaler.⁴

If patients have ongoing poorly or partly controlled asthma with the use of an ICS/LABA inhaler

At any point in treatment, if patients with asthma have inadequate control of symptoms, as assessed by the Asthma Control Test, clinicians should consider whether other clinically relevant issues are contributing to a patient's symptoms (Stage two of the four-stage asthma consultation process). This can include factors such as a patient's inhaler technique or adherence, co-morbidities or exposure to factors in the home or work environment which are provoking a worsening of asthma control. Attention to correct inhaler technique is particularly important if patients have switched to a different type of inhaler when initiating ICS/LABA treatment. For some patients it may be appropriate to consider whether the diagnosis of asthma should be re-evaluated.

 For further information see "Managing adults with asthma in primary care: the four-stage consultation", www.bpac.org.nz/2017/asthma.aspx

If symptoms have not improved

Occasionally, patients may have no improvement in symptoms despite appropriate use of an ICS/LABA inhaler. If this is the case, the ICS/LABA inhaler can be discontinued and patients should be prescribed a high dose ICS preventer inhaler.⁴

If symptoms have improved but asthma control remains suboptimal

Treatment can be escalated by increasing the daily dose of ICS in the combination ICS/LABA inhaler, according to Step 4 of the New Zealand Adult Asthma Guidelines pharmacological treatment model (Tables 1 and 2). Emphasise to patients that their dose of preventer treatment is being increased but they should use the same doses for relief of acute symptoms as before. A subsidised combination ICS/LABA inhaler containing fluticasone furoate and vilanterol (Breo Ellipta) can be prescribed at Step 4 of the New Zealand Adult Asthma Guidelines. Fluticasone furoate is more potent than fluticasone propionate and at Step 4 is prescribed at a dose of 100 micrograms per day, compared to 500 micrograms per day of fluticasone propionate.

Patients who have ongoing symptoms at Step 4 may need to be initiated on additional treatments, such as sodium cromoglicate, sodium nedocromil, montelukast, theophylline or tiotropium; consider discussing these patients with a respiratory physician if they are not already receiving outpatient management.¹

 Patient information sheets for ICS/LABA inhalers are available from the New Zealand Formulary:

- Budesonide + formoterol: www.mymedicines.nz/home/sheet/Budesonide-and-formoterol
- Fluticasone + salmeterol: www.mymedicines.nz/home/sheet/Fluticasone-and-salmeterol

Acknowledgement: Thank you to **Professor Richard Beasley**, Respiratory Physician, Director of the Medical Research Institute of New Zealand, Wellington for expert review of this article.

References:

1. Beasley R, Hancox RJ, Harwood M, et al. Asthma and Respiratory Foundation NZ adult asthma guidelines: a quick reference guide. *N Z Med J* 2016;129:83–102.
2. Masoli M, Holt S, Weatherall M, et al. Dose-response relationship of inhaled budesonide in adult asthma: a meta-analysis. *Eur Respir J* 2004;23:552–8. doi:10.1183/09031936.04.00076604
3. Holt S, Suder A, Weatherall M, et al. Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. *BMJ* 2001;323:253–6.
4. British Thoracic Society, Scottish Intercollegiate Guidelines Network (SIGN). British guideline on the management of asthma. 2016. Available from: www.sign.ac.uk/pdf/SIGN153.pdf (Accessed Mar, 2017).
5. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2016. Available from: www.ginasthma.org (Accessed Feb, 2017).
6. Chowdhury BA, Dal Pan G. The FDA and safe use of Long-Acting Beta-Agonists in the treatment of asthma. *N Engl J Med* 2010;362:1169–71. doi:10.1056/NEJMp1002074
7. New Zealand Formulary (NZF). NZF v57. 2017. Available from: www.nzf.org.nz (Accessed Mar, 2017).
8. Thomas M, Pavord I. Single inhaler maintenance and reliever therapy (SMART) in general practice asthma management: where are we? *Prim Care Respir J* 2012;21:8–10. doi:10.4104/pcrj.2012.00022
9. Palmqvist M, Arvidsson P, Beckman O, et al. Onset of bronchodilation of budesonide/formoterol vs. salmeterol/fluticasone in single inhalers. *Pulm Pharmacol Ther* 2001;14:29–34. doi:10.1006/pupt.2000.0260
10. Kew KM, Karner C, Mindus SM, et al. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2013;12:CD009019. doi:10.1002/14651858.CD009019.pub2
11. Braithwaite I, Williams M, Power S, et al. Randomised, double-blind, placebo-controlled, cross-over single dose study of the bronchodilator duration of action of combination fluticasone furoate/vilanterol inhaler in adult asthma. *Respir Med* 2016;119:115–21. doi:10.1016/j.rmed.2016.09.006
12. National Institutes for Health and Care Excellence (NICE). Chronic asthma: management. Draft guidance. 2016. Available from: www.nice.org.uk/guidance/indevelopment/gid-cgwave0743/documents (Accessed Mar, 2017).
13. AstraZeneca Ltd. Symbicort. New Zealand data sheet. 2016. Available from: www.medsafe.govt.nz/profs/datasheet/s/Symbicortinh.pdf (Accessed Mar, 2017).
14. Brown RW, O'Brien CD, Martin UJ, et al. Long-term safety and asthma control measures with a budesonide/formoterol pressurized metered-dose inhaler in African American asthmatic patients: a randomized controlled trial. *J Allergy Clin Immunol* 2012;130:362–367.e9. doi:10.1016/j.jaci.2012.03.028
15. Corren J, Mansfield LE, Pertseva T, et al. Efficacy and safety of fluticasone/formoterol combination therapy in patients with moderate-to-severe asthma. *Respir Med* 2013;107:180–95. doi:10.1016/j.rmed.2012.10.025
16. Bremner P, Woodman K, Burgess C, et al. A comparison of the cardiovascular and metabolic effects of formoterol, salbutamol and fenoterol. *Eur Respir J* 1993;6:204–10.