

Budesonide with eformoterol dry powder inhaler (Symbicort Turbuhaler) maintenance and reliever regimen for asthma

(byoo-DES-oh-nide with ee-for-MOH-te-rol)

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Summary

- Replacing the usual short-acting beta₂ agonist reliever with extra, on-demand use of budesonide with eformoterol is a substantial change in asthma treatment. Though supported by clinical trial evidence, the new regimen's place in routine practice is not established.
- The extended PBS listing allows people who experience frequent asthma symptoms while receiving combination therapy or corticosteroids alone to use the alternative budesonide with eformoterol maintenance and reliever regimen.
- People with good asthma control should not switch to the new maintenance and reliever regimen. Some people with poor symptom control on combination therapy may benefit from the maintenance and reliever regimen as an alternative to increasing their maintenance doses.
- The new regimen may not be suitable for people who are poor perceivers of airway obstruction or who overuse relievers.
- Ensure that people:
 - have a suitable asthma action plan for the maintenance and reliever regimen
 - know to always use the combination inhaler for symptom relief rather than a blue reliever inhaler
 - know to monitor how often they use the inhaler
 - know not to take more than 6 inhalations on a single occasion, and no more than 12 inhalations per day.
- Eformoterol is a long-acting beta₂ agonist but has a rapid onset of action. Fluticasone with salmeterol (Seretide) cannot be used as a reliever because salmeterol has too slow an onset.
- Do not use the budesonide with eformoterol 400/12 strength inhaler for the maintenance and reliever regimen, because it can easily lead to overdosing.

PBS listing

Extended listing for Symbicort 100/6 and Symbicort 200/6 strengths only.

Restricted benefit

Single maintenance and reliever therapy for people who experience frequent asthma symptoms while receiving treatment with:

- inhaled or oral corticosteroids OR
- a combination of an inhaled corticosteroid and a long-acting beta₂ agonist.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended amending the current listing of budesonide with eformoterol 100/6 and 200/6 to include 'maintenance and reliever' therapy for people who had frequent asthma symptoms while taking oral or inhaled corticosteroids.¹ The PBAC noted that the 'maintenance and reliever' approach had clinical advantages (including fewer exacerbations compared with conventional combination treatment) at a potentially lower cost to the Pharmaceutical Benefits Scheme (PBS), with reduced oral corticosteroid use and a lower inhaled corticosteroid burden.²

The PBAC recommended the 20-day safety net rule should not apply, allowing pharmacists to supply a second inhaler soon after the first (e.g. so that people can keep one at home and one on their person).

Place in therapy

Budesonide with eformoterol combines an inhaled corticosteroid ('preventer') with a long-acting beta₂ agonist ('symptom controller'). Combination therapy is suitable for people who have experienced frequent asthma symptoms despite daily inhaled corticosteroids. Recent clinical trials support an alternative dosing regimen in which the person uses the combination inhaler both for regular maintenance doses and as a reliever in response to symptoms ('maintenance and reliever regimen'). There is not enough experience with the new regimen to assess its place in routine clinical practice, but in trials it reduced exacerbations at a lower average inhaled corticosteroid dose, compared with the conventional combination regimen. People with good asthma control should not switch to the new regimen.

Use combination therapy with an inhaled corticosteroid and a long-acting beta₂ agonist for moderate to severe persistent asthma not controlled adequately by an inhaled corticosteroid alone

Asthma treatment guidelines recommend step management based on asthma control (see Figure 1).^{3,4} Most people should only start combination therapy with

an inhaled corticosteroid and a long-acting beta₂ agonist if they experience frequent asthma symptoms on a low to moderate dose of inhaled corticosteroid monotherapy (with a short-acting beta₂ agonist as 'reliever'). Rule out poor adherence, poor inhaler technique and adverse effects of drugs for comorbidities before stepping up drug therapy.

Budesonide with eformoterol as both maintenance and reliever

Conventionally, an inhaled corticosteroid and a long-acting beta₂ agonist are used at a regular daily dose to maintain asthma control, with a short-acting beta₂ agonist ('reliever') used as required for intermittent symptoms. The budesonide with eformoterol 'maintenance and reliever regimen' is an alternative to this conventional approach. It uses a combination budesonide with eformoterol inhaler both for maintenance dosing and on demand to relieve symptoms, with no use of a short-acting beta₂ agonist inhaler (the maker of Symbicort refers to this regimen as 'Symbicort maintenance and reliever therapy', or SMART).

Recently, a series of clinical trials found that people who had persistent asthma symptoms despite regular inhaled corticosteroids experienced significantly fewer severe exacerbations when following the maintenance and reliever regimen compared with the conventional combination regimen.⁵⁻⁸ Table 1 summarises the results of COMPASS, the only published double-blind trial where the maintenance and reliever regimen was compared with a higher-dose conventional regimen.⁵

Figure 1. Step care of persistent asthma⁴

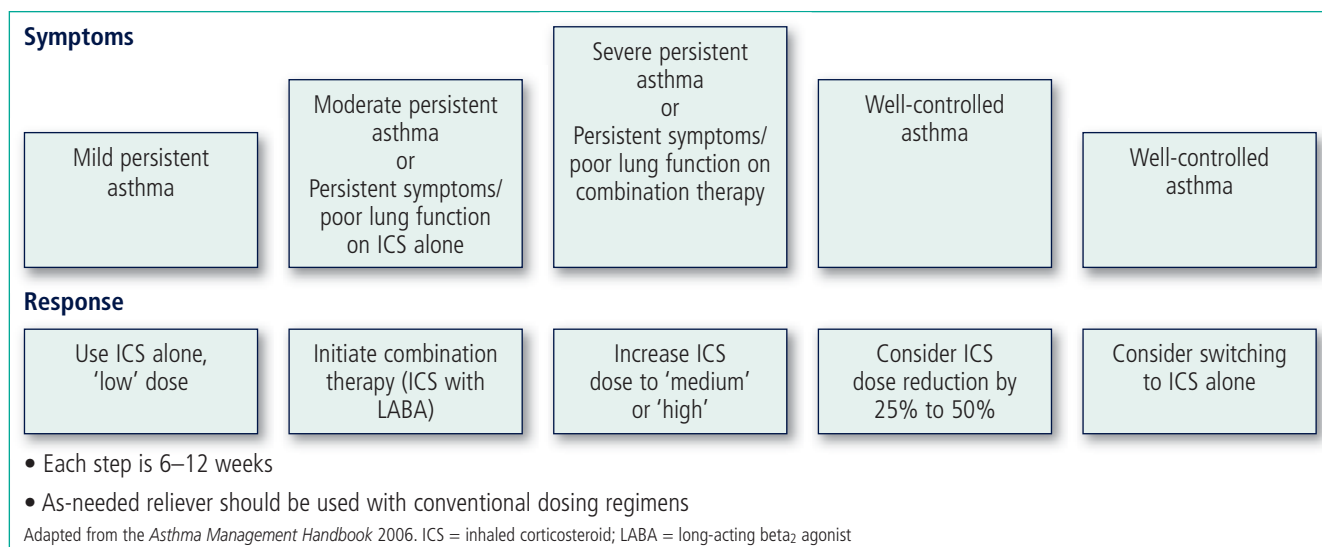


Table 1: Rates of severe asthma exacerbations in the COMPASS trial⁵

Treatment group	Severe exacerbations per 100 patients per 6 months	Average daily ICS dose (budesonide equivalent)*
Budesonide with eformoterol (maintenance and reliever regimen) n = 1107	12 [†]	604
Budesonide with eformoterol (conventional regimen) n = 1105	16	800
Fluticasone with salmeterol (conventional regimen) n = 1123	19	800

* This article reports metered doses (as is usual in Australia), while the COMPASS publication reports delivered doses. A budesonide with eformoterol metered dose of 200 micrograms/6 micrograms is equivalent to a delivered dose of 160 micrograms/4.5 micrograms.

† The number of severe exacerbations was significantly less than with the budesonide with eformoterol conventional regimen ($p = 0.0048$) and also significantly less than with the fluticasone with salmeterol conventional regimen ($p < 0.001$).

Switching people to a new dosing regimen is potentially confusing and could result in medication under- or over-use. Nonetheless, the trial results suggest that people with poor symptom control despite already using an inhaled corticosteroid at medium to high dose will benefit by changing to the new regimen. The regimen may also be useful when other strategies to rectify inhaled corticosteroid under-use have failed. The revised PBS listing allows for a switch directly from any inhaled corticosteroid or inhaled corticosteroids with long-acting beta₂ agonist combination (e.g. fluticasone with salmeterol inhaler [Seretide]) to the budesonide with eformoterol maintenance and reliever regimen.

There is limited experience with the maintenance and reliever regimen outside of clinical trials, and some practicalities remain uncertain. In particular, we do not know the best starting dose or the best approach to titrating up and down (see Dosing issues). In the general community the probabilities of inhaler under- or over-use may also differ from those observed in clinical trials.

Trials of the maintenance and reliever regimen did not allow for individual asthma action plans and self-management (e.g. to initiate oral corticosteroids), an approach that can improve asthma control.⁹ In addition, only one open-label trial (COSMOS) has compared the maintenance and reliever regimen with a maintenance dosing regimen in which the maintenance dose could be adjusted by the treating clinician. This study also found a significant reduction in the number of severe exacerbations over 12 months with the budesonide with eformoterol maintenance and reliever regimen, compared with conventional fluticasone with salmeterol (24 vs 31 exacerbations per 100 patient-years).⁸

Both the inhaled corticosteroid and long-acting beta₂ agonist components of the combination appear to contribute to efficacy when used on demand to relieve symptoms. In the SMILE trial all participants received the same maintenance dose of budesonide with eformoterol but were randomised to an on-demand inhaler consisting of either terbutaline (a short-acting beta₂ agonist), eformoterol, or budesonide with eformoterol. There were fewer severe asthma exacerbations in the eformoterol group than in the terbutaline group, and fewer again in the budesonide with eformoterol group.⁷

There is no evidence to support using the maintenance and reliever regimen in chronic obstructive pulmonary disease (COPD), and budesonide with eformoterol does not have a PBS listing for this indication.

People who have good asthma control should not switch to the maintenance and reliever regimen

The clinical trials of the maintenance and reliever regimen did not include participants with good asthma control at recruitment. There are no demonstrated advantages in adherence or clinical outcomes to support changing stable patients onto the maintenance and reliever regimen.

The maintenance and reliever regimen may be unsuitable for people who are poor perceivers of airway obstruction or who overuse relievers

The maintenance and reliever regimen with budesonide/ eformoterol may be unsuitable for some people because of the way they respond to changes in their asthma.¹⁰ People who overuse their reliever because of anxiety,

habit or because they are unfit, rather than because of poor asthma control, may be prone to over-treatment, exposing them to inhaled corticosteroid adverse effects with the new regimen. People who deliberately avoid using their reliever despite experiencing asthma symptoms, or who do not use their reliever because they cannot perceive airway obstruction, may have an increased risk of exacerbations with the new regimen (because the on-demand inhalations contribute to preventing severe exacerbations).

If there is a discrepancy between a patient's reported reliever use and other measures of asthma control, the patient may be under- or over-using their reliever. This pattern may only become apparent over several consultations. Lung function testing may assist in identifying poor perceivers and over-users, and specialist referral may be helpful in hard-to-manage cases.

Adherence benefits and cost savings for patients have not been demonstrated

Depending on the individual level of as-needed use, patient out-of-pocket costs may be higher or lower with the maintenance and reliever regimen, compared with using a separate short-acting beta₂ agonist reliever. Although the maintenance and reliever regimen may be more convenient for some people, it has no demonstrated adherence benefits, and other strategies (e.g. increased follow-up or patient education) should be used to improve adherence when this is known to be a problem.¹¹

Safety issues

In trials the maintenance and reliever regimen did not alter the incidence or severity of adverse events, but clinical experience is limited. Ask patients to monitor their inhaler use, both to measure asthma control and to prevent the possibility of excessive dosing. Note that fluticasone with salmeterol (Seretide) inhalers **cannot** be used in a maintenance and reliever regimen.

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse reactions, see the Therapeutic Goods Administration website (www.tga.gov.au).

Do not use the budesonide with eformoterol 400/12 strength inhaler for the maintenance and reliever regimen

The budesonide with eformoterol 400/12-strength inhaler is not indicated or PBS listed for the maintenance and reliever regimen. If people use the 400/12-strength inhaler 'as needed', they can easily exceed the recommended maximum daily dose of budesonide and eformoterol (2400 micrograms/72 micrograms), increasing the risk of adverse effects. People who require a daily maintenance dose of budesonide > 800 micrograms/day as part of combination therapy should use the conventional regimen.

The maintenance and reliever regimen may decrease the inhaled corticosteroid burden

In 1 open-label trial (COSMOS) that allowed for dose titration of the maintenance component, the total mean daily inhaled corticosteroid dose was 13% lower with the maintenance and reliever regimen than with the conventional regimen.⁸ No conclusions can be drawn about relative inhaled corticosteroid burden from the large double-blind trials because the maintenance and reliever regimen was compared with a fixed-dose conventional regimen, in which there was no possibility to titrate maintenance doses up or down.⁵⁻⁷

Although on average the maintenance and reliever regimen may decrease the inhaled corticosteroid burden, some people will use more on-demand inhalations than others. In the COMPASS trial, 17% of the patients assigned to the maintenance and reliever regimen used on average more than 800 micrograms/day of budesonide.⁵

Ask people using the maintenance and reliever regimen how often they use the inhaler for relief of symptoms. Patients should monitor inhaler use as part of their asthma action plan (see Dosing issues). Using more than 6 inhalations per day as a reliever may indicate poor asthma control and may also increase the risk of adverse effects due to high doses of budesonide or eformoterol. The manufacturer recommends that people should never take more than 6 inhalations on a single occasion, and up to a total of 12 inhalations per day only temporarily.¹²

The maintenance and reliever regimen did not change the incidence of non-asthma adverse effects in trials

In trials of the maintenance and reliever regimen there were no clinically important differences between treatment arms in the incidence, type and severity of non-asthma adverse events. In 2 trials the total incidence of typical inhaled corticosteroid and long-acting beta₂ agonist adverse events was 2–6%.^{6,7} Across all trials the incidence of reported adverse events was low, so small differences in adverse event rates between the regimens cannot be ruled out.

Patients risk under-medication if they substitute a short-acting beta₂ agonist for the combination inhaler

As any extra inhalations for symptom relief contribute to patients' total daily inhaled corticosteroid intake, there is a risk of under-medication with inhaled corticosteroid if a short-acting beta₂ agonist is used instead of the combination inhaler. People using the maintenance and reliever regimen in the COMPASS trial received on average about one-third of their budesonide intake from on-demand combination inhaler use.⁵ Advise people who are accustomed to the over-the-counter availability of short-acting beta₂ agonist inhalers (blue relievers) that they will need to change their routine (see Information for patients).

Fluticasone with salmeterol (Seretide) cannot be used for the maintenance and reliever regimen because salmeterol has too slow an onset of action

Only budesonide with eformoterol has been studied in the maintenance and reliever regimen. Eformoterol, although long-acting, has an onset of bronchodilation similar to that of salbutamol.^{13,14} The other long-acting

beta₂ agonist available in Australia, salmeterol (Serevent), has a slower onset and takes 10–20 minutes to have a substantial effect.¹⁴ For this reason, fluticasone with salmeterol (Seretide) should only be used in a conventional dosing regimen together with a short-acting beta₂ agonist as reliever.

Dosing issues

When changing to the maintenance and reliever regimen, start with a maintenance dose in the 'low' to 'medium' range of inhaled corticosteroid doses, titrating upwards if necessary to achieve good control, and downwards after symptoms are controlled. The goal remains to find the minimum effective dose of inhaled corticosteroid that maintains asthma control.

Start the maintenance and reliever regimen using Symbicort 200/6

There have been no clinical trials comparing different maintenance doses in the maintenance and reliever regimen, but the principles of step care support the use of an initial dose of budesonide 200–400 micrograms/day ('low' dose range) for moderate persistent asthma and 400–800 micrograms/day ('medium' dose range) or higher for severe persistent asthma.⁴ In clinical trials of the maintenance and reliever regimen, the most common maintenance dose was budesonide 400 micrograms/ eformoterol 12 micrograms per day.^{5–8}

The product information recommends using the maintenance and reliever regimen with a daily maintenance dose of either 2 inhalations of the 200/6 strength inhaler or a lower dose of 2 inhalations of the 100/6 strength.¹² Some people may require a higher daily maintenance dose of 4 inhalations of the 200/6 strength.¹² The 100/6 strength is suitable for people with a lower initial inhaled corticosteroid requirement and for back-titration when asthma is well controlled.

Table 2: Budesonide with eformoterol maintenance and reliever regimen maintenance dosing¹²

Inhaler strength for maintenance and relief	Twice-daily maintenance dosing	Once-daily maintenance dosing	Total daily maintenance dose (micrograms)
100/6	1 inhalation, morning and evening	2 inhalations, morning or evening	200/12
200/6	1 inhalation, morning and evening	2 inhalations, morning or evening	400/12
200/6	2 inhalations, morning and evening	—	800/24

Table 3: Responding to increases in reliever use with the maintenance and reliever regimen¹⁵

Daily inhalations of budesonide with eformoterol	Patient actions
> 12 inhalations (total) in any day	See a doctor or go to hospital the same day
> 6 reliever inhalations a day over 2–3 days*	Recommended actions could include: <ul style="list-style-type: none"> • measure peak flow and/or • start a course of prednisolone and/or • contact a doctor

* This threshold is based on an unpublished analysis of exacerbations in clinical trials and has not been validated prospectively

Twice-daily maintenance dosing was used in trials and is consistent with the conventional regimen, but once-daily dosing is also possible for the lower doses. See Table 2 for dosing options. Although some maintenance dosing options involve taking 2 inhalations at a time, do not substitute a higher-strength inhaler to reduce patient costs.

The old PBS listing for the budesonide with eformoterol inhaler required that people first used a separate long-acting beta₂ agonist inhaler until they had achieved a stable dose. However, in clinical trials of the maintenance and reliever regimen, many people switched directly from inhaled corticosteroid-only maintenance onto the budesonide with eformoterol fixed-dose combination inhaler.^{5–8} The revised PBS listing allows this, as well as switching directly from other combination regimens.

Ensure that people have an up-to-date asthma action plan

The maintenance and reliever regimen requires a specific written asthma action plan that differs from conventional plans. Asthma action plan templates for the maintenance and reliever regimen are available on the National Asthma Council website (www.nationalasthma.org.au/html/management/action_plans/ap005.asp) and are also included in Medical Director prescribing software.

The templates for asthma action plans that are included in the *Asthma Management Handbook* require adaptation to be used for the maintenance and reliever regimen.

The maintenance and reliever regimen depends on the person responding to worsening asthma by increasing their use of the combination inhaler. In addition, the action plan should make it clear how to respond to more serious increases in asthma symptoms and reliever use

(see Table 3). Tailor the action plan according to the pattern of the person’s asthma and the extent to which they wish to manage their own medication use. People with a history of rapid-onset deterioration may need to take action at lower numbers of inhalations than described in Table 3 and the asthma action plan template.

Back-titrate the maintenance dose to the minimum that maintains asthma control

When asthma has been well controlled for 6–12 weeks, consider reducing the maintenance dose by decreasing the number of maintenance inhalations per day or switching from the 200/6 strength inhaler to the 100/6 strength.

People who are stable and have good asthma control with 200 micrograms/day of budesonide or less can try discontinuing eformoterol, by switching to a budesonide-only inhaler (Pulmicort). To achieve this, people will need to switch to a conventional two-inhaler regimen with a separate reliever (salbutamol [Aiomir, Asmol, Epaq, Ventolin] or terbutaline [Bricanyl]). So far there is no documented clinical experience with switching between regimens in this way, and there is potential for patient confusion.

Information for patients

Explain all the details of the treatment regimen and the new asthma action plan. Make it clear which inhalers are being replaced; in most cases this will be the blue reliever, as well as the brown or orange preventer or purple combination inhaler. Make sure patients understand that even though the same inhaler is used both for regular daily treatment and as a reliever, this does not mean all doses are ‘as-needed’.

Suggest filling the first repeat soon after the original prescription when starting on the maintenance and reliever regimen because, unlike blue relievers, the combination inhaler is not available over the counter. As with any medication change, ask patients to come back after 1–3 months for review.

Advise patients:

- to take their regular maintenance treatment every day, even if they do not have any asthma symptoms
- to keep track of how often they use the inhaler for relief of symptoms and follow their asthma action plan when more inhalations are needed than usual
- to carry an inhaler to use as needed and to keep a second inhaler at home

- to replace inhalers when the red mark appears and to use a blue reliever only if their usual inhaler is unavailable
- not to take more than 6 inhalations on a single occasion, and never more than a total of 12 inhalations per day (maintenance plus reliever), because of the risk of side effects.

Suggest or provide the Symbicort consumer medicine information (CMI) leaflet (available at www.nps.org.au/consumers) for more information about side effects and how to use the inhaler.

References

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.