Fluticasone propionate with eformoterol fumarate (Flutiform) for asthma

(FLU-Ti-CAH-zone with EF-or-MOH-te-ROL)

KEY POINTS

Fluticasone-with-eformoterol fixed-dose combination (FDC) is indicated for people aged ≥ 12 years with asthma that cannot be adequately controlled with corticosteroids alone. Do not use for first-line treatment of asthma.

Fluticasone/eformoterol FDC has not been tested, and is not indicated, for use as a reliever or a combined preventer and reliever. Patients must have a short-acting beta-2-agonist reliever inhaler with them at all times.

Assess inhaler technique before prescribing and recommend that patients use a spacer. Fluticasone/eformoterol has only been tested in people considered to have good inhaler technique, and a spacer was used in the key trials.

Fluticasone/eformoterol FDC is comparable to the individual components administered separately for improving asthma control. In trials, asthma control was also improved to a similar extent with fluticasone/eformoterol compared with fluticasone/salmeterol and budesonide/eformoterol.

PBS listing

Restricted benefit

For patients who have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids and/or optimal doses of inhaled corticosteroids.

May be prescribed by nurse practitioners (shared care model)

Authorised nurse practitioners may prescribe this medicine within collaborative arrangements. See the PBS website for more information on nurse practitioner PBS prescribing.

What is it?

Fluticasone with eformoterol is an FDC pressurised metered-dose inhaler (pMDI) that combines the potent inhaled corticosteroid (ICS) fluticasone propionate and the selective long-acting beta-2-agonist (LABA) eformoterol fumarate. Fluticasone and eformoterol are well established individual therapies that are frequently prescribed for the treatment of asthma.1

When inhaled, fluticasone reduces airway inflammation and bronchial hyper-reactivity, and eformoterol relaxes bronchial smooth muscle by stimulating beta-2 adrenoceptors.2

Who is it for?

Fluticasone/eformoterol FDC treatment is indicated for people who have previously been started on an ICS or oral corticosteroids and are experiencing problems with asthma control and require the addition of a LABA (stepping up treatment).3

It is also suitable for people already using an ICS with a LABA (from separate or combination inhalers) who wish to switch treatments. Although these patients need to have been using an ICS, they do not need to have been stabilised on both individual components before they are eligible for this combination treatment.3
Not recommended for use in children under 12
This FDC therapy is indicated for adults and children ≥ 12 years. Fluticasone/eformoterol has only been tested in trial participants aged 12 and over. The highest dose of fluticasone/eformoterol (500 micrograms/20 micrograms twice daily) is only recommended for adults, as this has not been tested in people under 18.

Where does it fit?
Do not use fluticasone/eformoterol as first-line treatment
Treatment of asthma is a stepwise process that aims to achieve good asthma control by optimising the current level of control and minimising the risk of future adverse outcomes.

Patients unable to achieve good asthma control at the current level (step) of treatment should increase (step up) their medication intensity to achieve good asthma control (Figure 1). Use combination therapy with an ICS and a LABA for moderate to severe persistent asthma not controlled adequately by an ICS alone.

The Global Initiative for Asthma (GINA) defines clinical control of asthma as:
- No (twice a week or less) daytime symptoms
- No limitations of daily activities, including exercise
- No night-time symptoms or waking because of asthma
- No (twice a week or less) need for reliever treatment
- Normal or near-normal lung function
- No exacerbations

Fluticasone/eformoterol FDC is one treatment option
Fluticasone/eformoterol is one option; other FDCs available on the PBS for the treatment of asthma are budesonide/eformoterol (Symbicort) and fluticasone/salmeterol (Seretide).

Figure 1. Stepwise treatment of persistent asthma in adults

<table>
<thead>
<tr>
<th>STEP 1</th>
<th>STEP 2</th>
<th>STEP 3*</th>
<th>STEP 4</th>
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<tbody>
<tr>
<td><strong>Mild asthma</strong></td>
<td><strong>Mild asthma not controlled with SABA alone</strong></td>
<td><strong>Poorly controlled asthma in patients already taking an ICS</strong></td>
<td><strong>Severe asthma (requiring high-intensity treatment)</strong></td>
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<tr>
<td>SABA reliever* used as needed for symptom relief</td>
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<td>▶ SABA reliever* used as needed for symptom relief at ALL steps of treatment**&lt;sup&gt;5&lt;/sup&gt;</td>
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Add low-dose<sup>5</sup> ICS preventer<sup>1,5,7</sup>
Increase ICS dose from low to medium<sup>5</sup>
Continue low-dose ICS and add a LABA<sup>7</sup>
Switch to an ICS–LABA FDC formulation<sup>4</sup>

Continue with medium-dose ICS and add a LABA<sup>7</sup>
OR
Increase the ICS dose from low to medium to high and continue using a LABA<sup>5,7</sup>
OR
Consider higher-dose FDC formulations<sup>5</sup>

* Salbutamol 100–200 micrograms or terbutaline 500 micrograms by inhalation.<sup>5</sup>
† See Therapeutic Guidelines: Respiratory for details of total daily dose equivalents stratified as low, medium and high doses of ICS in adults.<sup>5</sup>
‡ Addition of a preventer is recommended if a SABA is needed more than twice a week to control asthma.<sup>5</sup>
§ Check the patient’s diagnosis, their inhaler technique and their adherence to current level of treatment before stepping up treatment.<sup>7</sup>
¶ Current PBS subsidies require that patients are stabilised on the individual components before they can start treatment with fluticasone/salmeterol or budesonide/eformoterol.
** If using budesonide/eformoterol as maintenance plus reliever treatment, use of an additional SABA is not indicated.

EVIDENCE SNAPSHOT

WHAT IS KNOWN ABOUT THIS DRUG?
Fluticasone with eformoterol is an FDC preventer pMDI that combines the ICS fluticasone propionate and the LABA eformoterol fumarate. This FDC is non-inferior\(^a\) for asthma control compared with:

- fluticasone and eformoterol used at the same time from separate inhalers
- fluticasone/salmeterol combination treatment as an FDC
- budesonide/eformoterol combination treatment as an FDC.

In trials, the incidence of adverse events with fluticasone/eformoterol was similar to that with each of the above comparators.

\(^{a}\) Non-inferior: the effect of a new drug is not worse than that of another drug by more than a pre-specified margin.

AREAS OF UNCERTAINTY
No data are available to guide switching between FDCs and it has not been shown whether fluticasone/eformoterol in FDC form improves adherence.

WHAT DOES NPS SAY?
LABA–ICS fixed-dose combination therapies are a convenient option for people for whom a LABA with an ICS is indicated, and should reduce the incidence of people using LABAs without an ICS, but may increase the incidence of people using the combination before an ICS alone has been trialled.

Fluticasone/eformoterol is one such FDC option. Efficacy for improving lung function is non-inferior to that of its individual components used together and to that of the other FDCs, fluticasone/salmeterol and budesonide/eformoterol.

LABA–ICS fixed-dose combinations must be used at the correct place in therapy, after an ICS alone has been trialled. Fluticasone/eformoterol is neither TGA approved nor PBS listed, for treatment of COPD or for use as a combined preventer and reliever; patients need a SABA reliever available at all times in case of an exacerbation.

Not approved for use as a reliever
Fluticasone/eformoterol FDC is indicated for use as a combined maintenance/preventer medication. This FDC therapy is neither TGA approved nor PBS listed for use as a reliever, and people using it also need to have a SABA reliever inhaler with them at all times.\(^4\) It is not approved for use as a single maintenance and reliever therapy and was not tested as such in the key trials, where salbutamol was used as a reliever.\(^9–11\)

Not for the treatment of COPD
Unlike its individual components, fluticasone/eformoterol FDC is neither TGA approved nor PBS listed for the treatment of COPD.\(^4\)

Educating and training patients is important
Educate patients to detect and manage deteriorating asthma, and in the optimal use of their medication, by providing them with information about asthma and inhaler technique (including a spacer if used) and the importance of self-monitoring.\(^5\)
Instruct patients in the proper use and care of the inhaler and assess the patient’s inhaler technique before starting treatment and at least 6-monthly thereafter. Correct use of the inhaler is essential for successful treatment. Advise patients to read the Consumer Medicine Information.

Use of a spacer is recommended

A suitable spacer should be used for asthma treatment with all MDIs. Spacers improve dose delivery and also lower the amount of drug deposited in the mouth, reducing the incidence of adverse events such as oropharyngeal candidiasis (thrush). As with other inhalers, retitrate to the lowest effective dose after adding a spacer.

The AeroChamber Plus spacer was used in the key trials with the fluticasone/eformoterol FDC. The AeroChamber Plus is a small-volume spacer device.

Provide patients with a written asthma action plan

Self-management plans that include a written asthma action plan reduce unscheduled doctor visits and hospitalisations for asthma. Select an action plan appropriate for the person’s age, educational status, language and culture. A range of different written asthma plans is available, including the National Asthma Council of Australia Asthma Action Plan.

Review at least annually

Review asthma severity and treatment at least annually. Review patients at treatment step 4 at least every 3 months even if their asthma is well controlled.

See Therapeutic Guidelines: Respiratory and the Asthma Cycle of Care for further details on reviewing asthma treatment.

How does it compare?

Efficacy of the three different doses of fluticasone/eformoterol FDC was assessed in a series of non-inferiority studies. The studies demonstrated that the FDC is non-inferior to fluticasone and eformoterol used together from separate inhalers, budesonide/eformoterol FDC and fluticasone/salmeterol FDC for improving asthma control.

These studies measured improvement in lung function (FEV₁) over 8–12 weeks with different treatments and treatment doses. Treatments met the definition for non-inferiority if the lower limit of the confidence interval of the mean change in FEV₁ from baseline to the end of treatment was within 0.2 L. Only participants who demonstrated good inhaler technique were included in the key studies.

Three studies compared the efficacy of fluticasone/eformoterol FDC with other treatment options for improving lung function from baseline to pre-dose at the end of treatment. A fourth study investigated the change in FEV₁ from baseline to 30–60 minutes post dose at the end of treatment.
Fluticasone propionate with eformoterol fumarate (Flutiform)

Asthma control with fluticasone/eformoterol FDC is non-inferior to that of individual components used together

Improvement in asthma control in people taking high-dose fluticasone/eformoterol FDC (500 micrograms/20 micrograms) twice daily was non-inferior to that in people using fluticasone (500 micrograms) and eformoterol (24 micrograms) twice daily together from separate inhalers.⁵

This was shown in the intention-to-treat and the per-protocol trial populations of an 8-week, randomised, double-blind double-dummy study (n = 620). Trial participants were aged ≥ 18 years and were being treated with ≥ 500 micrograms of fluticasone or equivalent ICS dose* per day (most were already taking ICS (> 98%) and a LABA (75.5%)) before the study.¹⁰

The efficacy of fluticasone/eformoterol FDC at low (100 microgram/10 microgram) and medium (250 microgram/10 microgram) doses used twice daily was shown to be non-inferior to that of the individual components — fluticasone (100 micrograms) plus eformoterol (12 micrograms) or fluticasone (250 micrograms) plus eformoterol (12 micrograms) — used together twice daily from separate devices in a 12-week, open-label observational study (n = 210).¹¹ This was shown in the per-protocol treatment group and the full-analysis-set treatment group.¹¹

Trial participants were aged ≥ 12 years with mild to moderate–severe, persistent asthma and were randomised then assigned a treatment dose based on their pre-trial drug requirements.¹¹

Incidence of other symptoms

Incidence of other outcomes reflective of asthma control, such as night-time waking, mean asthma symptom scores, percentage of days without asthma symptoms and use of rescue medication, was similar between people using high-dose combination treatment and people using high doses of fluticasone and eformoterol together from separate inhalers.¹⁰

Incidence of outcomes including sleep disturbance scores, use of rescue medication and mean asthma symptom scores was also similar between people using low- and medium-dose fluticasone/eformoterol FDC and the equivalent components used together from separate inhalers.¹¹ However, these additional outcomes were not the primary outcomes of the studies.¹²,¹³

The incidence of asthma exacerbations (investigated as a secondary outcome) was also similar between people using high-dose FDC treatment (36.4%) and those using high-dose fluticasone and eformoterol together from separate inhalers (35.3%),¹⁰,²⁴

Incidence of serious exacerbations was similar between people using low- or medium-dose fluticasone/eformoterol FDC or the equivalent components used together from separate inhalers (occurring in 3.8% and 2.9% of participants, respectively).¹¹

Improved adherence not shown in the key trials

Good medication adherence was defined in the key studies as ≥ 75% and was achieved by more than 90% of trial participants.⁸–¹¹ Trial data indicate similar levels of adherence for people using fluticasone/eformoterol FDC compared with the different comparators.⁸–¹¹ However, investigating adherence was not a primary outcome of the studies.⁸–¹¹

Safety issues

Safety data for use of fluticasone/eformoterol combination treatment in people previously using an ICS comes mainly from the key trials.⁸–¹¹

As with other FDC formulations, it is important that people are aware which of their current medications are being replaced and that they discontinue use of these individual medicines. People using fluticasone/eformoterol FDC do need to have a SABA reliever available at all times, as this treatment has not been tested, and is neither TGA approved nor PBS listed, for use as a reliever.
Fluticasone propionate with eformoterol fumarate (Flutiform)

NPS RADAR | DECEMBER 2013

ADDITIONAL INFORMATION

Australian Government Department of Human Services:

Show patients which medicines are being replaced and advise them to return unneeded medicines to a pharmacy for safe disposal. This will reduce the risk of medicine errors. A Home Medicines Review may also be helpful for some patients.25 See the Australian Government Department of Human Services web page for further details of Home Medicines Reviews.

For information about reporting adverse reactions to the TGA, or to report suspected adverse reactions online, see the TGA website (www.tga.gov.au/safety/problem.htm#medicine) or use the ‘Blue Card’ distributed with the October issue of Australian Prescriber.

Incidence of adverse events

Adverse events and drug–drug interactions that patients may experience when taking fluticasone/eformoterol FDC are expected to be similar to those associated with using the individual components.4

In the key trials, incidence of adverse events, including severe adverse events, was similar with fluticasone/eformoterol FDC compared with that for the individual components used together from separate inhalers, and to that for fluticasone/salmeterol FDC and budesonide/eformoterol FDC.8–11

Adverse events reported by ≥ 1% of people taking fluticasone/eformoterol FDC in phase 3 trials are listed in the Product Information and include bronchitis, nasopharyngitis, exacerbation of asthma symptoms, and headache.4

Oropharyngeal candidiasis is a common adverse event associated with use of ICS medicines.2 Use of a spacer with the inhaler will lower the amount of drug deposited in the mouth and reduce the risk of adverse events such as thrush.4,5,7

Bronchospasm may occur

As with other inhalation treatments, bronchospasm may occur, leading to an immediate increase in wheezing after dosing. If this occurs, advise patients to treat immediately with their SABA reliever, stop taking this combination therapy and seek an assessment by their health professional. An alternative treatment should be started if needed.4

Good asthma control during pregnancy and breastfeeding is paramount

Optimal asthma control during pregnancy is vital for the mother and baby and a harm–benefit assessment should be undertaken for each patient.26

Fluticasone/eformoterol FDC therapy has not been tested in pregnant or breastfeeding women in adequate or well-controlled studies.4 As individual components, fluticasone and eformoterol are rated as Australian category B3 for use in pregnancy.2

Switching to a budesonide-based treatment is recommended for women planning a pregnancy, as it is a category A rated drug.6 However, to reduce the risk of an exacerbation during pregnancy, women should continue with the same medication they used before they became pregnant, especially if this treatment controlled their asthma.6

Review asthma control in these patients monthly.26

Prolonged treatment may result in adrenal suppression and acute adrenal crisis

Adrenal suppression can occur with high doses of ICS.2,4 Treatment should not be stopped suddenly in these patients.2 Consider the need for additional corticosteroids during periods of stress.2,4

Avoid use with potent CYP3A4 inhibitors

Avoid using fluticasone/eformoterol with potent CYP3A4 inhibitors such as protease inhibitors, clarithromycin and itraconazole.4

Concomitant use increases the risk of systemic adverse events, as fluticasone is a substrate of CYP3A4 and a marked increase in plasma levels of fluticasone is expected.4

Inhaled fluticasone used with ritonavir has been associated with Cushing’s syndrome and adrenal suppression.4,27

People taking potent CYP3A4 inhibitors within the last week were excluded from key trials.8,9,11
Fluticasone propionate with eformoterol fumarate (Flutiform)

PBAC: Pharmaceutical Benefits Advisory Committee

Ensure good inhaler technique
Skill and training are required when using pMDIs to coordinate the activation of the inhaler and inhalation. A spacer should be used with all pMDIs; the Aero Chamber Plus spacer is recommended for use with this inhaler.

Reason for PBS listing
The PBAC recommended the listing of fluticasone with eformoterol pMDI for maintenance treatment of asthma on a cost-minimisation basis with fluticasone/salmeterol pMDI.

Dosing issues
Fluticasone/eformoterol combination therapy is available in three fixed-dose combinations:

- Fluticasone (50 micrograms)
  - Eformoterol (5 micrograms)
- Fluticasone (125 micrograms)
  - Eformoterol (5 micrograms)
- Fluticasone (250 micrograms)
  - Eformoterol (10 micrograms).

Each treatment contains 120 actuations, which represents 60 doses (one dose is two actuations); each dose should be inhaled twice daily. Discard and replace the inhaler after 30 days.

The effect of one actuation of these formulations is not known and if the patient’s dose is to be stepped down, prescribe a different formulation. Use the lowest effective dose (see Figure 1).

Use of a spacer with the device is recommended (see ‘Use of a spacer is recommended’, page 16).

Doses in adults and children aged 12 years or over
The recommended dose for adults and children aged ≥12 years is two inhalations of the 50 microgram/5 microgram formulation twice daily, unless the person has severe asthma, in which case they should start on two inhalations of 125 micrograms/5 micrograms twice daily (the 50 microgram/5 microgram formulation is not appropriate for adults or children with severe asthma). Patients whose asthma remains poorly controlled on the 50 microgram/5 microgram strength may be stepped up to two inhalations of the 125 microgram/5 microgram FDC twice daily.

Adults whose asthma remains poorly controlled on this dose may be stepped up to two inhalations of the 250 microgram/10 microgram FDC twice daily.

Do not use the highest dose formulation in children under 18 years
The highest dose of the fluticasone/eformoterol FDC (two inhalations of the 250 microgram/10 microgram FDC twice daily) has not been tested in people <18 years and is not recommended for use in these people.

Children under 12 and elderly patients
Fluticasone/eformoterol combination treatment is not approved for use in children under 12.

No specific dose adjustments are required in elderly patients although data reflecting the efficacy and safety in this specific population are not available.
Information for patients

Advise patients as follows:

➤ rinse their mouth or gargle with water, or brush their teeth, after every dose to minimise the risk of candida yeast-like infection

➤ the inhaler (and the spacer) are to be used, and cleaned, as advised and as directed in the CMI and stored below 25°C but should not be refrigerated or frozen

➤ fluticasone/eformoterol FDC must be used daily for optimal benefit, even when they are asymptomatic

➤ the inhaler must not be used more often than is recommended

➤ the dose is two inhalations (actuations) twice daily

➤ use a suitable spacer with this inhaler (one puff of medication into the spacer at one time, use the ‘one deep breath’ or ‘four normal breaths’ technique, then repeat for the second inhalation)

➤ fluticasone/eformoterol combination therapy is not approved for use as a reliever, and a SABA must be accessible at all times and used if symptoms occur between doses

➤ an additional LABA must not be used under any circumstances; unneeded medicines (which are replaced by this FDC) should be returned to a pharmacy for safe destruction

➤ if they experience serious asthma-related adverse events while using fluticasone/eformoterol they should continue treatment but seek medical advice

➤ if they begin to need to use their reliever (SABA) more frequently, to return to their doctor immediately to have their treatment reviewed

➤ discard and replace the inhaler after 30 days.

Discuss the fluticasone propionate with eformoterol fumarate (Flutiform) Consumer Medicine Information (CMI) leaflet with the patient.

An NPS Medicine Update article on Flutiform is available for consumers at www.nps.org.au/medicine-update/flutiform. Medicine Update helps consumers to ask the right questions about new medicines and helps them compare the potential benefits and harms of a new medicine with those of other medicines.
Fluticasone propionate with eformoterol fumarate (Flutiform)

NPS RADA | DECEMBER 2013

REFERENCES


REFERENCES Continued


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NPS RADAR articles may be updated when there is new evidence about safety or efficacy, or in case of regulatory or PBS listing changes.

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