

Fluticasone propionate with salmeterol xinafoate (Seretide) for chronic obstructive pulmonary disease

(FLOO-tikka-zown, sal-MET-ah-roll)

Summary

- The PBS listing of fluticasone with salmeterol has been extended to include the symptomatic treatment of COPD in people with FEV₁ < 50% of predicted normal, and a history of repeated exacerbations with significant symptoms despite regular beta₂ agonist treatment.
- Fluticasone with salmeterol is not PBS listed for initiating bronchodilator therapy in people with COPD.
- Only the fluticasone with salmeterol 250/25 metered-dose inhaler and 500/50 dry powder inhaler preparations are PBS listed for COPD.
- Fluticasone with salmeterol has been shown to improve FEV₁ and reduce exacerbations more than either fluticasone or salmeterol given alone in moderate to severe COPD.
- If there is no clinically significant response to fluticasone with salmeterol after 4–8 weeks, discontinue treatment.
- Fluticasone with salmeterol could be considered in moderate to severe COPD with symptoms that are poorly controlled despite regular beta₂ agonist treatment after considering the balance of potential benefits and harms — high-dose inhaled corticosteroids may be beneficial but can cause significant adverse effects, including pneumonia.

PBS listing

Restricted benefit

Fluticasone with salmeterol was previously listed on the Pharmaceutical Benefits Scheme (PBS) as a restricted benefit for the treatment of asthma.¹

Fluticasone with salmeterol doses (microgram/microgram)	Formulation	PBS listed for COPD
50/25	MDI	
125/25	MDI	
250/25	MDI	✓
100/50	DPI	
250/50	DPI	
500/50	DPI	✓

This listing has been extended to the symptomatic treatment of chronic obstructive pulmonary disease (COPD) in people with forced expiratory volume in 1 second (FEV₁) < 50% of predicted normal, and a history of repeated exacerbations with significant symptoms despite regular beta₂ agonist treatment. The listing only applies to fluticasone with salmeterol 250/25 metered-dose inhaler (MDI) and 500/50 dry powder inhaler (DPI) preparations (Table 1), reflecting the submission to the Pharmaceutical Benefits Advisory Committee (PBAC). Fluticasone with salmeterol is not listed for initiating bronchodilator therapy in people with COPD.²

Reason for PBS listing

The PBAC recommended a restricted benefit listing on a cost-minimisation basis — that is, similar efficacy and cost — with fluticasone 500 micrograms and salmeterol 50 micrograms twice daily being considered equi-effective to tiotropium 18 micrograms inhaled once daily in the treatment of COPD. Tiotropium is the only long-acting bronchodilator monotherapy subsidised on the

PBS for COPD¹ and thus was considered an appropriate comparator. However, anticholinergic bronchodilators (such as tiotropium) have a different mechanism of action to those of inhaled corticosteroids and/or long-acting beta₂ agonists. The PBAC did not accept that fluticasone with salmeterol was more cost-effective — that is, offered greater effectiveness warranting a higher cost — compared with tiotropium.

Place in therapy

Consider fluticasone with salmeterol for people with COPD who have FEV₁ < 50% of predicted normal and symptoms that are poorly controlled despite regular beta₂ agonist treatment. Fluticasone with salmeterol has been shown to improve FEV₁ and reduce exacerbations more than either fluticasone or salmeterol given alone in moderate to severe COPD.^{4–6} However, there are no published head-to-head studies comparing these outcomes between fluticasone with salmeterol and tiotropium.

Clinical guidelines recommend stepped care for stable COPD

Drug treatments for COPD have not been shown to modify the decline in lung function, but they can improve symptoms and quality of life.^{7,8}

The usual stepped care approach^{6–10} includes:

- Step 1: intermittent short-acting bronchodilators (beta₂ agonist or anticholinergic) as needed.*
- Step 2: if there is no change in symptoms, regular inhaled bronchodilators (short- or long-acting anticholinergic with or without a beta₂ agonist†). Discontinue treatment if there is no clinically significant response after 4–8 weeks. People with most response to long-acting beta₂ agonists have some reversible airflow limitation.¹¹
- Step 3: an inhaled corticosteroid‡ is suggested for people with:
 - FEV₁ ≤ 50% of predicted normal and/or
 - more than 2 exacerbations per year requiring treatment with antibiotics or oral corticosteroids.

Discontinue treatment if there is no clinically significant response after 4–8 weeks.

Combining an inhaled corticosteroid with a long-acting beta₂ agonist may provide some additional benefit for people with moderate to severe COPD

Fluticasone with salmeterol has been shown to improve FEV₁ more than either fluticasone or salmeterol given alone in people with moderate to severe COPD.⁴

Combined therapy with an inhaled corticosteroid and a long-acting beta₂ agonist reduces acute exacerbations.⁶ A meta-analysis showed that combining an inhaled corticosteroid with a long-acting beta₂ agonist[§] reduced exacerbations in moderate to severe COPD by about 30% (relative risk 0.70, 95% confidence interval [CI] 0.62 to 0.78) — slightly more than the 20–25% reduction seen with either long-acting beta₂ agonists (RR 0.79, 95% CI 0.69 to 0.90) or inhaled corticosteroids, respectively (RR 0.76, 95% CI 0.72 to 0.80).⁵

The same meta-analysis showed that fluticasone with salmeterol had no effect on mortality.⁵ A recent 3-year study (in which about 40% of people discontinued treatment) showed a trend towards a reduced mortality for fluticasone with salmeterol (12.6%) compared with placebo (15.2%) but this did not reach statistical significance (RR 0.83, 95% CI 0.68 to 1.00, *p* = 0.052).¹²

Assess response to combined therapy by monitoring symptoms and FEV₁; stop if there is no clinically significant response after 4–8 weeks.^{6–10} Only people who show clear and clinically significant benefit should continue treatment, because of the potential risks.

Safety issues

Only high-dose inhaled corticosteroids are effective in moderate to severe COPD^{13,14}; high doses increase the risk of adverse effects, including:

- oropharyngeal candidiasis and dysphonia.^{3,14,15}

* Short-acting bronchodilators are subsidised on the PBS for COPD.¹

† Long-acting beta₂ agonists are not subsidised on the PBS for initiation of bronchodilator therapy or for symptomatic relief in COPD. Tiotropium is the only long-acting bronchodilator subsidised on the PBS for COPD.¹

‡ Inhaled corticosteroids are not approved by the TGA for COPD. They are listed on the PBS general schedule as unrestricted benefits and prescribers may write prescriptions in line with their clinical judgment.^{1,3}

§ The combinations included were fluticasone with salmeterol, and budesonide with formoterol.

- adrenal impairment, skin thinning and bruising, osteoporosis, cataracts and glaucoma, particularly in older people.^{3,6,15} Recent data from people with moderate to severe COPD suggested there were no differences in fracture rates or cataract development between those receiving fluticasone with salmeterol and those receiving placebo.¹²
- pneumonia. Recent data in people with moderate to severe COPD showed that for every 17 people treated for 3 years with fluticasone (instead of salmeterol alone), 1 extra person will develop pneumonia (19.6% compared with 13.3%)¹² — the elderly who take inhaled corticosteroids have a higher risk of pneumonia hospitalisation.¹⁶

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online (see www.tgasime.health.gov.au) 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).

Dosing issues

The usual starting dose for fluticasone in COPD is 250 micrograms by inhalation, twice daily.⁶ Fluticasone should be titrated to the lowest dose at which effective control of symptoms is maintained.³ The usual dose for salmeterol in COPD is 50 micrograms by inhalation, twice daily.⁶ However, the PBS-listed dose is fluticasone 500 micrograms with salmeterol 50 micrograms inhaled twice a day.² This can be delivered as either 250/25 micrograms via MDI or 500/50 micrograms via DPI preparations.¹⁵

Combination inhalers have limited dosing flexibility

COPD is a condition that changes over time, so dose adjustments may be required that are not possible with the combination MDI or DPI.⁶ Ideally, treatment should

be initiated with single-ingredient preparations of fluticasone and salmeterol to allow assessment of response and dose adjustment of each drug (as recommended by guidelines^{6–10} before moving to the combination MDI or DPI. Some people may be better managed with separate fluticasone and salmeterol inhalers; however, these are not PBS listed for COPD.¹

Information for patients

Advise patients:

- that adverse effects of the combination MDI or DPI appear to be similar to those of the individual components
- to rinse their throat and mouth with water and spit out after each dose to reduce the risk of oral candida infection and/or systemic absorption of fluticasone
- to use a spacer if using an MDI, to reduce the risk of adverse effects
- to use this medicine as prescribed every day, even if feeling well, and not to stop taking it suddenly.

Suggest or provide the Seretide consumer medicine information (CMI) leaflet (available at www.nps.org.au/consumers).

Medicine Update

An NPS *Medicine Update* leaflet on fluticasone with salmeterol is available for consumers. *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 other medicines.

References

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Correction August 2008: Footnote on PBS listing of inhaled corticosteroids revised.

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.