Overview of medicines used in asthma management and an index to information on each class of asthma medicine, and medicines in sport

ABOUT

This PDF is a print-friendly reproduction of the content included in the Resources – Medicines guide section of the Australian Asthma Handbook at asthmahandbook.org.au/resources/medicines-guide

Please note the content of this PDF reflects the Australian Asthma Handbook at publication of Version 1.2 (October 2016). For the most up-to-date content, please visit asthmahandbook.org.au

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ABBREVIATIONS

CFC  chlorofluorocarbon
COPD  chronic obstructive pulmonary disease
COX  cyclo-oxygenase
ED  emergency department
EIB  exercise-induced bronchoconstriction
FEV₁  forced expiratory volume over one second
FVC  forced vital capacity
FSANZ  Food Standards Australia and New Zealand
GORD  gastro-oesophageal reflux disease
HFA  formulated with hydrofluoroalkane propellant
ICS  inhaled corticosteroid
ICU  intensive care unit
IgE  Immunoglobulin E
IV  intravenous
LABA  long-acting beta₂-adrenergic receptor agonist
LAMA  long-acting muscarinic antagonist
LTRA  leukotriene receptor antagonist
MBS  Medical Benefits Scheme
NIPPV  non-invasive positive pressure ventilation
NSAIDs  nonsteroidal anti-inflammatory drugs
OCS  oral corticosteroids
OSA  obstructive sleep apnoea
PaCO  carbon dioxide partial pressure on blood gas analysis
PaO₂  oxygen partial pressure on blood gas analysis
PBS  Pharmaceutical Benefits Scheme
PEF  peak expiratory flow
pMDI  pressurised metered-dose inhaler or ‘puffer’
SABA  short-acting beta₂-adrenergic receptor agonist
TGA  Therapeutic Goods Administration

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ENDORSEMENT

The Australian Asthma Handbook has been officially endorsed by:

• The Royal Australian College of General Practitioners (RACGP)
• The Australian Primary Health Care Nurses Association (APNA)
• The Thoracic Society of Australia and New Zealand (TSANZ)

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Medicines guide

Overview

Asthma medicines are classified by their role in asthma management (preventers and relievers) as well as by their pharmacological and chemical classes. Preventers include combination preventers (inhaled corticosteroid and long-acting beta₂ agonist combinations).

Other medicines used in asthma management are neither relievers nor preventers, but have specific roles in the management of flare-ups, severe acute asthma, or difficult-to-treat asthma.

The main pharmacological classes of asthma medicines are beta₂ receptor agonists, corticosteroids and leukotriene receptor antagonists.

Note: Pharmaceutical Benefits Scheme restrictions are stated within the guidance on asthma management, where relevant.

Table. Classification of asthma medicines

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- **Reliever medicines**
  Guide to reliever medicines

- **Preventer medicines**
  Guide to preventer medicines

- **Systemic corticosteroids**
  Guide to systemic corticosteroids

- **Other asthma medicines**
  Guide to other asthma medicines

- **Medicines in sport**
  Guide to use of asthma medicines in sport
### Table. Classification of asthma medicines

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<th>Pharmacological class</th>
<th>Agent</th>
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<td>Short-acting beta(_2) agonist relievers</td>
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<td>Terbutaline sulfate</td>
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<td>Inhaled corticosteroid/rapid-onset long-acting beta(_2)</td>
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<td>Short-acting muscarinic antagonists * (in acute asthma, or as an alternative to a short-acting beta(_2) agonist)</td>
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<td>Magnesium sulfate</td>
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<td>Fluticasone furoate</td>
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<td>Inhaled corticosteroid/long-acting beta(_2) agonist</td>
<td>Budesonide/formoterol fumarate dihydrate</td>
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<td>combinations ‡</td>
<td>Fluticasone furoate/vilanterol trifenate ‡</td>
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<td>Use</td>
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<td>Pharmacological class</td>
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<td>Fluticasone propionate/formoterol fumarate dihydrate&lt;br&gt;Fluticasone propionate/salmeterol xinafoate</td>
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<td>Leukotriene receptor antagonists</td>
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<td>Sodium cromoglycate&lt;br&gt;Nedocromil sodium</td>
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<td>Other add-on medicines for long-term use</td>
<td>Anti-immunoglobulin E (IgE)</td>
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<td>Anti-interleukin-5 (IL-5)</td>
<td>Mepolizumab</td>
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<td>Long-acting muscarinic antagonist *§</td>
<td>Tiotropium bromide</td>
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<td>Long-acting beta₂ agonists #</td>
<td>Formoterol fumarate dihydrate&lt;br&gt;Salmeterol xinafoate</td>
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<tr>
<td></td>
<td>Theophyllines</td>
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* Muscarinic antagonists are also called anticholinergic bronchodilators.

§ For patients with asthma, long-acting muscarinic antagonists should be prescribed only in addition to an inhaled corticosteroid.

† The budesonide/formoterol fumarate dihydrate combination is used as reliever only for adolescents and adults for whom the maintenance-and-reliever regimen has been prescribed.

‡ Fluticasone furoate/vilanterol should be taken as one inhalation once daily. Warn patients not to take more inhalations or more frequent doses.

# For patients with asthma, long-acting beta₂ agonists should be prescribed only in combination with an inhaled corticosteroid.

Notes
Before prescribing any medicine, check the Therapeutic Goods Administration-approved product information.
Pharmaceutical Benefits Scheme criteria for some asthma medicines differ between age groups and indications.

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Guide to reliever medicines

Overview

Relievers are bronchodilator medicines used for rapid resolution of bronchoconstriction. They can also be used pre-emptively to prevent exercise-induced bronchoconstriction.

Every patient with asthma (or their carers) should:

- carry a reliever medicine at all times
- replace it whenever it reaches the expiry date.

Relievers contain rapid-onset beta$_2$ receptor agonists, which include:

- short-acting beta$_2$ agonists (salbutamol and terbutaline)
- the combination of an inhaled corticosteroid (budesonide) and long-acting beta$_2$ agonist (formoterol) in a single inhaler.
  
  This option only applies to patients using combination budesonide/formoterol in a maintenance-and-reliever regimen.

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More information

**Short-acting beta-2 agonist relievers for children: 0–5 years**

Inhaled short-acting beta$_2$ agonists are effective bronchodilators in children aged 0–5 years.$^1$

Short-acting beta$_2$ agonists may be less effective for wheezing in children under 2 years old than in older children.$^2$ However, many clinical trials in infants have included those with bronchiolitis, so there is limited evidence for the effects of short-acting beta$_2$ agonists specifically in asthma.$^2$ Studies conducted in emergency departments have shown that short-acting beta$_2$ agonists are more effective than placebo in controlling acute wheeze in children under 2 years, but may not achieve clinically significant improvements.$^2$

Paradoxical responses to inhaled short-acting beta$_2$ agonists have been reported in infants.$^1$ Bronchodilators are generally not recommended in children under 6 months old, consistent with current guidelines for the management of acute bronchiolitis.$^3$

Inhaled short-acting beta$_2$ agonists are generally well tolerated in children aged 0–5 years.$^1$ Adverse effects (e.g. muscle tremor, headache, palpitations, agitation or hypokalaemia) have been reported at high doses.$^3$

Oral short-acting beta$_2$ agonists are associated with adverse effects$^1$ and should not be used in any age group.

**Short-acting beta-2 agonist relievers for children: 6 years and over**

Inhaled short-acting beta$_2$ agonists are the major class of bronchodilators used for relief of symptoms in asthma.$^4$ They are the most effective bronchodilators available and are recommended by international guidelines for use in children of all ages as well as in adults.$^5$

Children with controlled asthma need little or no reliever (on no more than 2 days per week).

Increased use of short-acting beta$_2$ agonists for relief of asthma symptoms, especially daily use, indicates deterioration of asthma control.$^5,^6$
### Table. Definition of levels of recent asthma symptom control in children (regardless of current treatment regimen)

<table>
<thead>
<tr>
<th>Good control</th>
<th>Partial control</th>
<th>Poor control</th>
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<tr>
<td><strong>All of:</strong></td>
<td><strong>Any of:</strong></td>
<td><strong>Either of:</strong></td>
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</tbody>
</table>
| • Daytime symptoms\(^\dagger\) ≤ 2 days per week (lasting only a few minutes and rapidly relieved by rapid-acting bronchodilator)  
• No limitation of activities\(^\dagger\)  
• No symptoms\(^\$\) during night or when wakes up  
• Need for reliever\(^\#\) ≤ 2 days per week | • Daytime symptoms\(^\dagger\) > 2 days per week (lasting only a few minutes and rapidly relieved by rapid-acting bronchodilator)  
• Any limitation of activities\(^*\)  
• Any symptoms during night or when wakes up\(^\dagger\dagger\)  
• Need for reliever\(^\#\) > 2 days per week | • Daytime symptoms\(^\dagger\) > 2 days per week (lasting from minutes to hours or recurring, and partially or fully relieved by rapid-acting bronchodilator)  
• ≥ 3 features of partial control within the same week |

\(^\dagger\) e.g. wheezing or breathing problems  
\(^\dagger\) child is fully active; runs and plays without symptoms  
\(^\$\) including no coughing during sleep  
\(^\#\) not including short-acting beta\(_2\) agonist taken prophylactically before exercise. (Record this separately and take into account when assessing management.)  
\(^*\) e.g. wheeze or breathlessness during exercise, vigorous play or laughing  
\(^\dagger\dagger\) e.g. waking with symptoms of wheezing or breathing problems

**Note:** Recent asthma control is based on symptoms over the previous 4 weeks. Each child’s risk factors for future asthma outcomes should also be assessed and taken into account in management.

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**Short-acting beta-2 agonist relievers for adults and adolescents**

Short-acting beta\(_2\) agonists are used to:

- relieve asthma symptoms  
- prevent exercise-induced bronchoconstriction  
- relieve exercise-induced bronchoconstriction.

The duration of therapeutic effect is approximately 4 hours.

When using a pressurised metered-dose inhaler for salbutamol, the use of a large-volume spacer increases the proportion of drug delivered to the lung.\(^7\) For adults, it is not essential to use a spacer with salbutamol for day-to-day symptoms if adequate relief is obtained with a pressurised metered dose inhaler alone.

Patients with well-controlled asthma do not need to use their reliever on more than 2 days per week, not counting doses taken before exercise to prevent exercise-induced bronchoconstriction.

Increased use of short-acting beta\(_2\) agonists for relief of asthma symptoms, especially daily use, indicates worsening asthma control.\(^5,6\)
Note: Routine preventive doses of short-acting beta₂ agonist taken before exercise are not counted when assessing recent asthma symptom control. However, persistent exercise-induced bronchoconstriction generally indicates inadequate asthma control.

Table. Definition of levels of recent asthma symptom control in adults and adolescents (regardless of current treatment regimen)

<table>
<thead>
<tr>
<th>Good control</th>
<th>Partial control</th>
<th>Poor control</th>
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<tbody>
<tr>
<td>All of:</td>
<td>One or two of:</td>
<td>Three or more of:</td>
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<tr>
<td>• Daytime symptoms ≤2 days per week</td>
<td>• Daytime symptoms &gt;2 days per week</td>
<td>• Daytime symptoms &gt;2 days per week</td>
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<tr>
<td>• Need for reliever ≤2 days per week†</td>
<td>• Need for reliever &gt;2 days per week†</td>
<td>• Need for reliever &gt;2 days per week†</td>
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<tr>
<td>• No limitation of activities</td>
<td>• Any limitation of activities</td>
<td>• Any limitation of activities</td>
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<tr>
<td>• No symptoms during night or on waking</td>
<td>• Any symptoms during night or on waking</td>
<td>• Any symptoms during night or on waking</td>
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</tbody>
</table>

† Not including SABA taken prophylactically before exercise. (Record this separately and take into account when assessing management.)

Note: Recent asthma symptom control is based on symptoms over the previous 4 weeks.


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Over-use of short-acting beta-2 agonists

High use of short-acting beta₂ agonists may, itself, increase the risk of asthma flare-ups.⁸, ⁹

- Data from population and case-control studies has led to concerns that the frequent use of short-acting beta₂ agonists, including salbutamol, is associated with increased risk of asthma deaths.⁵ The risk of asthma deaths was greatest for fenoterol, which has since been withdrawn from use.⁸ For salbutamol, the risk is greatest for doses above 1000 mcg/day (10 puffs).
- Regular use of salbutamol 16 puffs/day (rather than as-needed use during symptoms) was associated with increased risk of asthma flare-ups requiring oral corticosteroids in a placebo-controlled clinical trial.¹⁰ Subsequent statistical modelling showed that the risk was associated with increased fluctuation in lung function.¹¹
- Regular use of short-acting beta₂ agonists leads to receptor tolerance (down-regulation) to their bronchoprotective and bronchodilator effects. Tolerance becomes more apparent with worsening bronchoconstriction. In severe asthma, this could result in a poor response to emergency treatment.¹²

When high doses of short-acting beta₂ agonist are needed (e.g. dose repeated at intervals of less than 4 hours in a person with acute severe asthma), the patient should be under medical supervision and should usually also be receiving systemic corticosteroids.

▶ See: Managing acute asthma in clinical settings

Combination budesonide/formoterol maintenance-and-reliever regimen in adults and adolescents: overview of efficacy

Low-dose budesonide/formoterol combination can be used as reliever for asthma symptoms (instead of using a short-acting beta₂ agonist reliever), in addition to its use as regular long-term preventer treatment.¹³, ¹⁴, ¹⁵, ¹⁶, ¹⁷, ¹⁸ The following formulations can be used in maintenance-and-reliever regimens:
• dry-powder inhaler (Symbicort Turbuhaler) 100/6 mcg or 200/6 mcg
• pressurised metered-dose inhaler (Symbicort Rapihaler) 50/3 mcg or 100/3 mcg.

Neither the 400/12 mcg dry-powder inhaler nor the 200/6 mcg pressurised metered-dose inhaler should be used in this way.

Overall, clinical trials show that budesonide/formoterol combination as maintenance and reliever reduces the risk of flare-ups that require oral corticosteroids, compared with other current preventer regimens and compared with a fixed higher dose of inhaled corticosteroids.¹⁹

Pooled data from five randomised controlled trials assessing budesonide/formoterol maintenance-and-reliever regimens showed that similar or better levels of asthma control were achieved with budesonide/formoterol maintenance-and-reliever compared with the conventional maintenance regimen comparators:¹⁵

• higher-dose budesonide
• same dose budesonide/formoterol
• higher-dose inhaled corticosteroid/long-acting beta₂ agonist (budesonide/formoterol or fluticasone propionate/salmeterol).

In randomised clinical trials in patients with a history of asthma flare-up within the previous 12 months (and therefore at greater risk of flare-up in the next 12 months), the use of formoterol/budesonide as maintenance-and-reliever regimen reduced the risk of asthma flare-ups that required treatment with oral corticosteroids, compared with the use of any of the following (plus a short-acting beta₂ agonist reliever as needed):¹⁵, ²⁰, ²¹

• the same combination as maintenance treatment only
• higher-dose combination as maintenance treatment only
• higher-dose inhaled corticosteroids.

Meta-analysis of six randomised controlled trials found that maintenance-and-reliever treatment with budesonide/formoterol reduced the risk of severe asthma flare-ups (use of oral corticosteroids for 3 days or more, hospitalisation or emergency department visits), compared with higher-dose inhaled corticosteroid alone, or in combination with a long-acting beta₂ agonist.²²

In open-label studies in which patients were not selected for a previous history of flare-ups, there was no overall difference in time to first flare-up between budesonide/formoterol as maintenance-and-reliever regimen and conventional maintenance regimens (including inhaled corticosteroid or inhaled corticosteroid/long-acting beta₂ agonist combinations, leukotriene receptor antagonists, xanthines or any other asthma medicines) with rapid-onset beta₂ agonist reliever (selected according to clinician’s choice).²³ However, the inhaled corticosteroid dose was higher with conventional maintenance regimens.

**Note:** The fluticasone propionate/formoterol combination is approved by the Therapeutic Goods Administration only for regular maintenance therapy.

### Beta-2 agonists for exercise-induced bronchoconstriction

Inhaled beta₂-adrenergic receptor agonists are the most effective medicines for short-term protection against exercise-induced bronchoconstriction and for accelerating recovery of lung function after exercise.²⁴

However, short-acting beta₂ agonists should only be taken intermittently (i.e. less than daily), as necessary for preventing exercise-induced bronchoconstriction or relieving exercise-induced bronchoconstriction.²⁴ Daily use of short-acting beta₂ agonists may actually increase the severity of exercise-induced bronchoconstriction.²⁴

### Beta-2 agonists for exercise-induced bronchoconstriction: doses

Intermittent short-acting beta₂ agonists administered by inhalation 5 to 20 minutes before exercise are effective in protecting against exercise-induced bronchoconstriction for 2–4 hours.²⁴ Salbutamol and terbutaline are equally effective.²⁴

Recommended doses are as follows:

- **salbutamol** 100–400 micrograms by inhalation, 15 minutes before exercise
- **terbutaline** 500–1000 micrograms by inhalation, 15 minutes before exercise.

The World Anti-Doping Agency (WADA) no longer requires a Therapeutic Use Exemption application for an athlete to use salbutamol (maximum 1600 mcg per day) or to declare use during drug testing.
- Terbutaline is prohibited by WADA. Exemption may be given in certain circumstances. WADA guidelines prohibit all beta2 agonists except salbutamol (maximum 1600 micrograms over 24 hours), formoterol (maximum 36 micrograms over 24 hours) and salmeterol when taken by inhalation in accordance with the manufacturers’ recommended therapeutic regime.
- When prescribing for competitive athletes, check which substances are permitted. Refer to ASADA or WADA for a current list of prohibited substances.

Go to: Australian Sports Anti-Doping Authority
Go to: World Anti-Doping Agency

**Salbutamol in acute asthma: dosing regimens**

One placebo-controlled study showed that, for patients who showed clear improvement after the first dose of salbutamol via pressurised metered-dose inhaler and spacer, there was no advantage in repeating the dose more often than every 60 minutes until full recovery (extra doses can be given as needed).

However, in patients who did not show a clear response to the first salbutamol dose, repeating the dose at intervals of 30 minutes or less was more effective than every 60 minutes.

**Salbutamol in acute asthma: route of administration**

**Inhaler plus spacer, or nebuliser**

Salbutamol delivered via a pressurised metered-dose inhaler with spacer is at least as effective as salbutamol delivered via nebuliser in patients with moderate-to-severe acute asthma who do not require ventilation. The use of nebulisers increases the risk of transmitting respiratory infections to staff and other patients.

**Intravenous salbutamol**

Overall, intravenous short-acting beta2 agonists do not appear to be superior to inhaled short-acting beta2 agonist.

Benefits have not been demonstrated in adults. Very limited evidence from one study suggested that the addition of IV salbutamol to inhaled salbutamol reduced recovery time in children with severe acute asthma in the emergency department.

However, there is a lack of consensus on the appropriate dose of IV salbutamol for children. Recommendations differ between guidelines in Australia and elsewhere. Doses have not been calculated based on age-specific pharmacokinetic and pharmacodynamic data. The doses recommended in guidelines are generally relatively higher than for adults on a micrograms per kilogram body weight basis.

Compared with inhaled salbutamol, intravenous salbutamol is associated with increased risk of adverse effects including tremor and hypokalaemia. Concomitant use of the inhalation and IV routes may increase the risk of salbutamol toxicity.

**Note:** Salbutamol concentrate for infusion is available in 5 mL ampoules containing salbutamol sulfate equivalent to 5 mg (1 mg/mL) salbutamol in a sterile isotonic solution (Ventolin obstetric injection). Salbutamol for injection is also available in ampoules of salbutamol sulphate equivalent to 500 mcg salbutamol in 1 mL sterile isotonic solution (Ventolin injection).

**Beta-2 receptor tolerance**

**Short-acting beta2 agonists**

In laboratory studies, regular use of short-acting beta2 agonists leads to receptor tolerance (down-regulation) to their bronchoprotective and bronchodilator effects.

In clinical trials, regular use of short-acting beta2 agonists is associated with greater instability of lung function and a higher risk of asthma flare-ups.

In clinical practice, frequent use of short-acting beta2 agonists may lead to worsening of asthma symptoms. This may be improved by deliberately reducing short-acting beta2 agonist use and, in some cases, using ipratropium bromide as an alternative reliever medicine medication to allow restoration of beta2-receptor responsiveness.

**Long-acting beta2 agonists**

In laboratory studies, regular use of long-acting beta2 agonists results in reduced duration of protection against airway hyperresponsiveness, and prolonged recovery of airway function after short-acting beta2 agonist, which is thought to be
due to receptor tolerance (down-regulation) of beta\textsubscript{2} receptors in bronchial smooth muscle and mast cells (evidence from laboratory studies).\textsuperscript{35} These findings have led to concerns about reduced effectiveness of beta\textsubscript{2} agonists when needed for preventing exercise-induced bronchoconstriction or reversing acute asthma due to trigger exposure.\textsuperscript{35} Sensitivity to short-acting beta\textsubscript{2} agonists returns to normal within 72 hours of stopping long-acting beta\textsubscript{2} agonist treatment.\textsuperscript{35}

However, the clinical effects of beta receptor tolerance in patients taking long-acting beta\textsubscript{2} agonists are unclear.\textsuperscript{36} Clinical trials assessing regular use of long-acting beta\textsubscript{2} agonists in combination with inhaled corticosteroids have not reported clinically significant adverse effects attributable to beta receptor tolerance.\textsuperscript{37} Two Emergency Department studies in patients with acute asthma did not observe increased risk of hospitalisation among those taking salmeterol.\textsuperscript{36, 39}

The use of budesonide/formoterol as a reliever may result in lower total use of beta\textsubscript{2} agonist compared with the use of short-acting beta\textsubscript{2} agonist relievers, based on a study in patients taking regular maintenance budesonide/formoterol, which monitored inhaler actuations electronically.\textsuperscript{20}

**Beta-2 agonists for exercise-induced bronchoconstriction: receptor tolerance**

Regular daily use of short-acting beta\textsubscript{2} agonists and long-acting beta\textsubscript{2} agonists results in loss of efficacy due to receptor tolerance (tachyphylaxis), regardless of whether these medicines are used in combination with an inhaled corticosteroid.\textsuperscript{24}

Laboratory studies suggest that receptor tolerance may result in:

- a reduction in the degree of protection against exercise-induced bronchoconstriction when a short-acting beta\textsubscript{2} agonist or long-acting beta\textsubscript{2} agonist is taken before exercise\textsuperscript{24}
- a reduction in the duration of protection against exercise-induced bronchoconstriction when a short-acting beta\textsubscript{2} agonist or long-acting beta\textsubscript{2} agonist is taken before exercise\textsuperscript{24}
- a reduction in the effectiveness of short-acting beta\textsubscript{2} agonist taken as reliever after exercise if the person experiences exercise-induced bronchoconstriction, seen as an increase in the time to recovery from the episode of bronchoconstriction.\textsuperscript{24}

Receptor tolerance may resolve within 72 hours of discontinuing a short-acting beta\textsubscript{2} agonist or long-acting beta\textsubscript{2} agonist.\textsuperscript{24}

**Implications for use of short-acting beta\textsubscript{2} agonists**

International consensus recommends against the over-use of short-acting beta\textsubscript{2} agonists.\textsuperscript{5}

**Implications for use of long-acting beta\textsubscript{2} agonists**

The evidence for adverse effects due to beta\textsubscript{2} receptor down-regulation in patients with asthma is unclear and the implications of current evidence are controversial.\textsuperscript{40, 41, 42} Most of the available evidence is from laboratory studies.

In adults, clinical trials and meta-analyses assessing regular use of long-acting beta\textsubscript{2} agonists in combination with inhaled corticosteroids indicate that the benefits outweigh the risks,\textsuperscript{43} but extremely large studies would be necessary to define the risk of very rare events.

There is evidence that the risk of adverse events associated with long-acting beta\textsubscript{2} agonist use (severe asthma episodes, hospitalisation, loss of effectiveness of short acting beta\textsubscript{2} agonists, and loss of protection against exercise-induced bronchoconstriction) may be higher in children than adults.\textsuperscript{40, 42} A beta\textsubscript{2} receptor genotype (Arg16 polymorphism in the beta\textsubscript{2} receptor gene) pre-disposes children with asthma to down-regulation of the beta\textsubscript{2} receptor and increased susceptibility to flare-ups during regular treatment with long-acting beta\textsubscript{2} agonists.\textsuperscript{44} A recent study in children with this genotype, and with asthma not adequately controlled despite inhaled corticosteroid treatment, demonstrated that the addition of montelukast was more effective than the addition of salmeterol.\textsuperscript{44} However, routine genetic testing to tailor asthma therapy is not yet available in clinical practice.

**References**


Guide to preventer medicines

Overview

Preventers are used in maintenance treatment to reduce airway inflammation. They include:

- inhaled corticosteroids (beclometasone, budesonide, ciclesonide, fluticasone propionate)
- combination inhaled corticosteroid/long-acting beta₂ agonist medicines (budesonide/formoterol, fluticasone furoate/vilanterol, fluticasone propionate/formoterol, fluticasone propionate/salmeterol)
- leukotriene receptor antagonists (montelukast)
- cromones (cromoglycate and nedocromil sodium).

Table. Classification of asthma medicines
Please view and print this figure separately: https://www.asthmahandbook.org.au/table/show/79

In this section

- **Inhaled corticosteroids**
  Guide to preventers: inhaled corticosteroids

- **Combinations**
  Guide to preventers: inhaled corticosteroid/long-acting beta-2 agonist combinations

- **Montelukast**
  Guide to preventers: montelukast

- **Cromones**
  Guide to preventers: cromones
Guide to preventers: inhaled corticosteroids

Preventers are used in maintenance treatment to reduce airway inflammation. They include inhaled corticosteroids (beclometasone, budesonide, ciclesonide, fluticasone).

**Table. Classification of asthma medicines**

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More information

**Inhaled corticosteroids for children: overview**

The effectiveness of ICS in children appears to depend on several factors including the child’s age, which triggers are causing symptoms, wheezing phenotype, tobacco smoke exposure and genotype. Overall, inhaled corticosteroids seem to be more effective in older children and those with more severe disease. Early introduction of inhaled corticosteroid for children with recurrent wheeze does not prevent airway remodelling, improve long-term lung function or prevent the onset of persistent asthma, according to current evidence from long-term randomised controlled clinical trials in preschool children and school-aged children with intermittent or mild persistent asthma.

**Inhaled corticosteroids for children: 0–5 years**

In preschool children with episodic (viral) wheeze, limited available evidence suggests that regular treatment with inhaled corticosteroids does not reduce the risk of hospitalisation, flare-ups that require oral corticosteroid use, or reduce the frequency and duration of acute episodes. Inhaled corticosteroid treatment does not reduce these children’s risk of developing persistent wheeze by age 6 years. Regular treatment with inhaled corticosteroids improves wheezing, asthma symptoms and lung function and reduces flare-ups in infants and preschoolers with persistent (at least 6 months) wheezing or asthma.

In preschool children with multiple-trigger wheeze, regular inhaled corticosteroids are moderately effective in controlling symptoms, but less effective than in older children. When multiple-trigger wheeze improves markedly during a short treatment trial (e.g. 3 months), it is not possible to tell whether improvement was due to the treatment or natural resolution of symptoms.

**Inhaled corticosteroids for children: 6 years and over**

Most clinical trials of regular inhaled corticosteroid treatment in children have been conducted among children with persistent asthma. Beclometasone dipropionate, budesonide, ciclesonide and fluticasone propionate have all been shown to be effective in children. However, there have been relatively fewer studies of ciclesonide (a newer inhaled corticosteroid) but, overall, randomised clinical trials show that it is equally effective as budesonide or fluticasone propionate in improving asthma symptoms and reducing flare-ups.

In school-aged children with mild persistent asthma, regular low-dose daily inhaled corticosteroid treatment reduces the rate of flare-ups that require treatment with oral corticosteroids, compared with no regular treatment and as-needed short-acting beta2 agonist for wheezing episodes.

The Thoracic Society of Australia and New Zealand’s current position statement on the use of inhaled corticosteroids in children recommends regular treatment with inhaled corticosteroid for school-aged children with moderate-to-severe persistent asthma, or those with frequent intermittent asthma or mild persistent asthma if symptoms are not controlled by a 2- to 4-week treatment trial with a cromone (nedocromil or sodium cromoglycate) or montelukast.

**Inhaled corticosteroids for adults: overview**
Inhaled corticosteroid preventer medicines available in Australia

The following inhaled corticosteroids are registered by the TGA:

- beclometasone dipropionate (low to high doses available)
- budesonide (low to high doses available, including in combination with a long-acting beta₂ agonist)
- ciclesonide (low to high doses available)
- fluticasone furoate (medium to high doses available, including in combination with a long-acting beta₂ agonist)
- fluticasone propionate (low to high doses available, including in combination with a long-acting beta₂ agonist)

Table. Definitions of ICS dose levels in adults

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<tr>
<td>Fluticasone propionate</td>
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</table>

† Dose equivalents for Qvar (TGA-registered CFC-free formulation of beclometasone dipropionate).
*Fluticasone furoate is not available as a low dose. TGA-registered formulations of fluticasone furoate contain a medium or high dose of fluticasone furoate and should only be prescribed as one inhalation once daily.

Note: The potency of generic formulations may differ from that of original formulations. Check TGA-approved product information for details.

Sources


Clinical benefits

Inhaled corticosteroids are the most effective preventer medicines for adults. Inhaled corticosteroids are effective in reducing asthma symptoms, improving quality of life, improving lung function, decreasing airway hyperresponsiveness, controlling airway inflammation, reducing the frequency and severity of asthma flare-ups, and reducing the risk of death due to asthma.

Most adults with asthma benefit from regular inhaled corticosteroid treatment

The current recommendation to initiate inhaled corticosteroid treatment for adults with asthma symptoms twice or more during the past month, or who experience waking due to asthma symptoms once or more during the past month, is based on consideration of clinical trial evidence that even patients with infrequent symptoms benefit from regular use of inhaled corticosteroids:

- In patients with recent-onset (diagnosis within 2 years) mild asthma (45% with symptoms 2 days/week or less), low-dose inhaled corticosteroid (budesonide 400 mcg/day) reduced the risk of severe flare-ups, increased symptom-free
days and lung function, and protected against long-term decline in lung function associated with severe asthma flare-ups (evidence from a 5-year large randomised clinical trial).  

- In small clinical trials in adults with symptoms or reliever use twice per week or less, the use of regular inhaled corticosteroids (fluticasone propionate 250 mcg/day) improved lung function, reduced airway hyperresponsiveness and inflammation, and reduced the risk of mild flare-ups.

The current recommendation replaces the previous higher threshold for inhaled corticosteroid treatment (asthma symptoms three times a week or more, or waking at least one night per week with asthma symptoms), which was based on consensus.

**Clinical benefits are achieved with low doses**

Low doses of inhaled corticosteroids are sufficient to achieve benefits in most patients:

- Regular use of low-dose inhaled corticosteroids reduced the risk of hospitalisation for acute asthma and death due to asthma (evidence from a large population cohort study). In that study, breaks in the use of inhaled corticosteroid of up to 3 months were associated with increased risk of death.
- In adults and adolescents with mild asthma who were not taking inhaled corticosteroids, starting low-dose inhaled corticosteroid (budesonide 200 mcg/day) reduced the risk of asthma flare-ups severe enough to require oral corticosteroids, and improved symptom control (evidence from a large clinical trial).
- In patients with recent-onset (diagnosis within 2 years) mild asthma (45% with symptoms 2 days/week or less), low-dose inhaled corticosteroid (budesonide 400 mcg/day) reduced the risk of severe flare-ups, increased symptom-free days and lung function, and protected against long-term decline in lung function associated with severe asthma flare-ups (evidence from a 5-year large randomised clinical trial).

**Note:** PBS status as at October 2016: Fluticasone furoate is not subsidised by the PBS, except in combination with vilanterol.

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**Inhaled corticosteroids for children: doses**

In the majority of children, asthma control can be achieved with any of the following initial doses:

- budesonide 400 mcg/day
- beclometasone (Qvar) 200 mcg/day
- ciclesonide 160 mcg/day
- fluticasone propionate 200 mcg/day.

If these doses do not achieve control of symptoms, possible explanations include alternative diagnoses, adherence, incorrect inhaler technique, psychosocial factors and exposure to tobacco smoke or other triggers such as allergens.

Dose–response studies of inhaled corticosteroids show that the maximal efficacy is generally achieved at a dose equivalent to approximately 200 mcg/day fluticasone propionate, while the risk of adrenal suppression increases exponentially at doses above 500 mcg/day. Therefore (based on theoretical equivalents between different agents), upper limits of daily doses for children are:

- budesonide 800 mcg/day
- beclometasone dipropionate (Qvar) 400 mcg/day
- ciclesonide 320 mcg/day
- fluticasone propionate 500 mcg/day.

Higher doses are unlikely to be more effective, and are likely to cause systemic effects.

Most studies of inhaled corticosteroids in children have used twice-daily dosing. Ciclesonide is effective when given once daily. The dose of inhaled corticosteroid delivered to the lungs will depend on many factors, including the delivery device, the age of the child, individual variation in inhaler technique, and adherence.

**Note:** Do not use beclometasone dose recommendations from outdated or overseas guidelines based on older formulations containing CFC propellant – doses are different.

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**Table. Definitions of ICS dose levels in children**

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Inhaled corticosteroids for adults: doses

Most of the benefit of inhaled corticosteroid is achieved with doses at the upper limit of the low-dose range (i.e. equivalent to 400 mcg budesonide per day, 200 mcg HFA beclometasone, 160 mcg ciclesonide or 200 mcg fluticasone propionate).

On average, higher doses provide relatively little extra benefit, but are associated with a higher risk of adverse effects. However, a small proportion of individuals may need a higher dose to achieve asthma control.

The recommendation to start inhaled corticosteroid at low dose is based on the following evidence.

A meta-analysis of results from randomised controlled trials comparing different doses of inhaled corticosteroids showed:

- An effective starting dose is 200–400 mcg/day for fluticasone propionate, 400–800 mcg/day for budesonide, or 200–400 mcg/day beclometasone.
- A starting dose higher than 800 mcg/day budesonide, 400 mcg/day fluticasone propionate, or 400 mcg beclometasone does not provide enough clinical benefit over lower doses to warrant routinely starting with high doses.
- Starting with a moderate dose of inhaled corticosteroid is as effective as commencing with a high dose and down-titrating. Although it may be reasonable to use a high starting dose then reduce the dose, down-titration cannot be ensured in practice (e.g. if the person does not return for planned review).
- High doses of inhaled corticosteroids may be more effective than a moderate or low dose for controlling airway hyperresponsiveness, but this may not equate to a clinical benefit.

Meta-analyses of inhaled corticosteroid safety have shown that the risk of local adverse effects (e.g. hoarseness, oral candidiasis) and the risk of systemic adverse effects (e.g. changes in hypothalamic-pituitary-adrenal function) increase significantly at higher doses. The risk of adrenal suppression should be considered whenever high doses are used (particularly of more potent inhaled corticosteroids), or when the patient uses concomitant medicines that inhibit cytochrome P450 (e.g. ritonavir, erythromycin or ketoconazole).

Notes

Dose equivalent for beclometasone applies to Qvar CFC-free formulation. Other brands may differ.

Do not use beclometasone dose recommendations from outdated or overseas guidelines based on older formulations containing CFC propellant – doses are different.

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† Dose equivalents for Qvar (TGA-registered CFC-free formulation of beclometasone dipropionate)
‡ Ciclesonide is registered by the TGA for use in children aged 6 and over

Source
Asset ID: 21
Inhaled corticosteroids for children: adverse effects

Topical
Hoarseness and pharyngeal candidiasis are not commonly reported among preschool children when using a metered-dose inhaler with spacer,\(^4\) or among school-aged children.\(^2\)

Inhaled corticosteroids, particular dry-powder formulas with pH < 5.5, may dissolve tooth enamel in children.\(^2\)

Topical effects can be reduced by use of spacer devices (which reduce oropharyngeal deposition), and by mouth-rinsing and spitting after use.\(^2\) Immediate quick mouth-rinsing removes more residual medicine in the mouth than delayed rinsing.\(^27\)

Systemic
Systemic effects of inhaled corticosteroids in children depend on the dose, but clinically significant adverse effects are uncommon.\(^2\) The use of spacers and mouth rinsing will not reduce systemic effects, but may increase efficacy so that a lower dose is required.

Short-term suppression of linear growth has been demonstrated in children, but only minimal long-term effects on growth or bone density have been reported.\(^2\) Some children may experience delay in the normal pubertal growth spurt due to asthma itself.\(^2\) Treatment beginning before puberty is associated with a small (mean approximately 1 cm) reduction in adult height.\(^28\)

A research study using biochemical testing in a research setting showed that hypothalamic–pituitary–adrenal axis suppression may occur in up to two-thirds of children treated with inhaled corticosteroids, and may occur at even low doses.\(^29\) However, clinically cases are rare.
Cases of symptomatic, clinically significant adrenal insufficiency in children due to inhaled corticosteroid treatment have been reported, including cases in Australia. Most cases have involved children given more than 500 mcg per day fluticasone propionate.

The risk of hypothalamic–pituitary–adrenal axis suppression is higher among children receiving concomitant intranasal steroids and those with lower body mass index. Risk is lower in obese children.

There are no nationally accepted protocols for routine assessment of adrenal function because it has not yet been possible to identify precisely which children should be tested, to interpret test results reliably, to identify the appropriate interval for retesting, and because a clinical benefit has not been clearly demonstrated.

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Inhaled corticosteroids for adults: adverse effects

Local adverse effects
Hoarseness (dysphonia) and candidiasis are the most common local adverse effects of inhaled corticosteroids with both pressurised metered-dose inhalers and dry-powder inhalers:

- The rate of dysphonia among patients taking inhaled corticosteroids has been estimated at 5–20%. However, higher rates of up to 58% have been reported in some studies. The risk varies with the device used.
- The rate of oropharyngeal candidiasis among adults using inhaled corticosteroids has been estimated at 5–7%, with positive mouth culture for Candida albicans in approximately 25% of patients. However, higher rates of up to 70% have been reported in some studies. The risk depends on the formulation, dose and dose frequency.

When taking inhaled corticosteroids via pressurised metered-dose inhalers, the use of a spacer reduces the risk of dysphonia and candidiasis. Spacers improve delivery of the medicine to the airways.

Rinsing the mouth with water after inhaling reduces the risk of oropharyngeal candidiasis. Quick mouth rinsing immediately after inhaling effectively removes a high proportion of remaining medicine.

The incidence of dysphonia and candidiasis is significantly lower with ciclesonide than with equivalent doses of fluticasone propionate. This may an important consideration for patients who experience dysphonia, particularly for those for whom voice quality is important (e.g. singers, actors, teachers). With ciclesonide, the rate of adverse effects may not differ when taken with or without a spacer.
Systemic adverse effects

Cross-sectional population studies have reported lower bone mineral density with long-term use of high doses of inhaled corticosteroid, but the effect on fracture risk in patients with asthma is unclear.

A meta-analysis of randomised controlled trials in adults older than 40 years with COPD (in which osteoporosis is more common) or asthma found no association between the use of inhaled corticosteroid and fracture risk overall, but found a slight increase in fracture risk among those using high doses.

Cross-sectional studies show a dose–response relationship between inhaled corticosteroid use for asthma or COPD, and risk of cataracts in adults.

Long-term inhaled corticosteroid use for asthma or COPD is associated with a small increase in the risk of developing diabetes, and in the risk of diabetes progression. These risks are greatest at higher doses (equivalent to fluticasone propionate 1000 mcg/day or higher).

The incidence of osteoporosis, cataracts and diabetes increases with age, and these conditions are also more common in smokers and in patients with COPD. Few studies have assessed risk specifically in patients with asthma.

Patients at risk of osteoporosis should be referred for bone density screening, screened for vitamin D and/or calcium deficiency, and provided with advice about maintaining bone health.

Patient concerns about adverse effects

The prevalence of side effects that patients consider troubling increases with increasing dose of inhaled corticosteroids. Mid and high doses are consistently associated with a higher intensity and a higher prevalence of reported adverse effects, after controlling for other factors.

A high proportion of people with asthma may have misunderstandings and fears about using inhaled corticosteroids, such as fears about weight gain, unwanted muscle development, bone fractures, susceptibility to infections and reduction of efficacy of the medicine over time. Most people do not discuss their concerns about inhaled corticosteroid treatment with health professionals. Safety concerns are a major reason for poor adherence, particularly general concerns about corticosteroids rather than concerns about specific adverse effects.

Inhaled corticosteroids for adults and adolescents: particle size

Medicines with small particle size (CFC-free beclometasone [Qvar] and ciclesonide) achieve a greater proportion of medicine deposited in the lungs, and are potentially distributed more widely in the large, intermediate, and small airways. However, the clinical implications have not been established.

Randomised controlled trials comparing ciclesonide with fluticasone propionate in adults and adolescents have observed lower rates of patient-reported side-effects, and confirmed dysphonia and oral candidiasis, among patients using ciclesonide than among those using fluticasone propionate.

Pneumonia risk with inhaled corticosteroids in patients with COPD

In people with COPD, the risk of pneumonia is increased by the use of regular inhaled corticosteroids. Most of the available evidence is from patients treated with fluticasone propionate. Increased pneumonia rates have also been observed in studies of patients with COPD using fluticasone furoate/vilanterol. The higher dose of fluticasone furoate/vilanterol (Breo Ellipta 200/25 mcg) is not indicated for patients with COPD.

Increased risk of pneumonia with inhaled corticosteroids has not been established in patients with asthma. However, the risk of pneumonia in patients with co-existing asthma and COPD is unknown, so caution is advised, particularly if high doses are being considered.

Inhaled corticosteroids for exercise-induced bronchoconstriction

Inhaled corticosteroids taken regularly long term (4 weeks or more) are effective in reducing the frequency and severity of exercise-induced bronchoconstriction in 30–60% of people with asthma. The degree of protection experienced by individuals ranges from complete to minimal.
Patients may need to take inhaled corticosteroid for 12 weeks to experience maximal therapeutic effect.\textsuperscript{64} If exercise-induced symptoms have resolved, the person may no longer need to take a beta\textsubscript{2} agonist before exercise.\textsuperscript{61} However, some patients taking regular inhaled corticosteroids may still need to take short-acting beta\textsubscript{2} agonists before exercise.\textsuperscript{61} Few comparative studies have compared the effectiveness of inhaled corticosteroid with that of other classes of medicines.\textsuperscript{60}

**Inhaled corticosteroids in acute asthma**

**Inhaled corticosteroid treatment in acute care**
Clinical trial evidence does not support the use of inhaled corticosteroids in place of systemic corticosteroid treatment in the treatment of acute asthma.\textsuperscript{62}

Some randomised clinical trials suggest that inhaled corticosteroid treatment may reduce hospital admission rates when given in addition to systemic corticosteroids, but the evidence is conflicting.\textsuperscript{62} Overall, evidence from randomised clinical trials does not show that inhaled corticosteroid therapy achieves clinically important improvement in lung function or clinical scores when used in acute asthma in addition to systemic corticosteroids.\textsuperscript{62}

**Inhaled corticosteroid treatment in post-acute care**
Current standard follow-up treatment after acute asthma includes a course of systemic corticosteroids, and continuation of inhaled corticosteroids for patients already taking this treatment.

Overall, evidence from randomised clinical trials suggests that inhaled corticosteroid treatment, given at discharge from the emergency department after acute asthma, does not provide additional short-term benefit in patients who are also receiving oral corticosteroids.\textsuperscript{63}

Some randomised clinical trials suggest that high-dose inhaled corticosteroid treatment at discharge from the emergency department may be as effective as oral corticosteroids in patients with mild acute asthma, but overall evidence does not support replacing oral corticosteroids with inhaled corticosteroids.\textsuperscript{63}

These clinical trials were designed to assess effects of inhaled corticosteroid in managing the current acute asthma episode. This evidence does not suggest that inhaled corticosteroids should be stopped after or during an acute asthma episode.\textsuperscript{63} Regular inhaled corticosteroid treatment is effective for preventing future flare-ups.\textsuperscript{16}

**Step-up options in children with asthma that is not controlled by low-dose inhaled corticosteroids**

In children whose asthma is inadequately controlled by low-dose inhaled corticosteroids alone (and adherence is good, inhaler technique is correct and diagnosis has been confirmed), treatment options include:

- increasing the inhaled corticosteroid dose
- adding montelukast
- switching to inhaled corticosteroid/long-acting beta\textsubscript{2} agonist combination.

<p>| Table. Step-up options for children when good asthma control is not achieved with low-dose ICS |
|---|---|---|
| <strong>Option</strong> | <strong>TGA-registered indications for add-on therapy</strong> | <strong>PBS considerations</strong> |
| <strong>High-dose ICS</strong> | N/A | Subsidised |
| <strong>ICS plus montelukast</strong> | 2 years and over | 2–5 years: not subsidised\textsuperscript{+} 6–14 years: not subsidised unless for exercise-induced bronchoconstriction despite ICS treatment\textsuperscript{†} 15 years and over: not subsidised\textsuperscript{‡} | |
| | 4 years and over for fluticasone propionate/ salmeterol xinafoate | Subsidised |</p>
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<td>12 years and over for budesonide/formoterol fumarate dihydrate</td>
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- Advise parents about potential adverse psychiatric effects of montelukast

* Montelukast is not subsidised for use in combination with other preventers or for children who require inhaled corticosteroids.

† Montelukast is subsidised for prevention of exercise-induced asthma if asthma is otherwise well controlled while taking optimal-dose inhaled corticosteroids – it is not otherwise subsidised in combination with inhaled corticosteroids (or inhaled corticosteroid/long-acting beta_{2} agonist combinations).

‡ Montelukast is not subsidised for people aged over 15 years.

In the majority of children with persistent asthma that requires preventive treatment, control can be achieved with one of these options.\(^2\)

**Increasing inhaled corticosteroid dose versus adding a long-acting beta_{2} agonist**

In children with persistent asthma taking regular inhaled corticosteroid, the addition of long-acting beta_{2} agonists improves lung function and reduces reliever use, compared with placebo or increasing the dose of inhaled corticosteroid, but does not appear to reduce the rate of asthma flare-ups requiring treatment with oral corticosteroids.\(^64,65,66\)

Overall, evidence from randomised clinical trials suggests that, for children and adolescents (aged 4–18 years) with persistent asthma that is inadequately controlled despite treatment with regular inhaled corticosteroids, increasing the dose of inhaled corticosteroid is equally effective as maintaining the inhaled corticosteroid dose but adding a long-acting beta_{2} agonist (i.e. switching to long-acting beta_{2} agonist/inhaled corticosteroid combination therapy) in in reducing the rate of asthma flare-ups that require treatment with systemic corticosteroids.\(^66\)

Children appear to benefit less from combination inhaled corticosteroid/long-acting beta_{2} agonist treatment than adolescents. In adolescents with persistent asthma that is not controlled by a low dose of inhaled corticosteroids, the combination of a long-acting beta_{2} agonist and an inhaled corticosteroid is modestly more effective in reducing the risk of flare-ups requiring oral corticosteroids than a higher dose of inhaled corticosteroids.\(^67\)

**Adding montelukast versus adding a long-acting beta_{2} agonist**

There is insufficient evidence from randomised clinical trials to determine, overall, whether adding a long-acting beta_{2} agonist or adding montelukast is more effective overall in children whose asthma is not controlled by regular inhaled corticosteroids.\(^68\)

Clinical response to long-acting beta_{2} agonists partly depends on genetics. A beta_{2} receptor genotype (Arg16 polymorphism in the beta_{2} receptor gene) pre-disposes children with asthma to down-regulation of the beta_{2} receptor and increased susceptibility to flare-ups during regular treatment with regular long-acting beta_{2} agonists.\(^69\) However, routine genetic testing to tailor asthma therapy is not yet available in clinical practice.

Among children 6 years and over with asthma that is not controlled by low-dose inhaled corticosteroids, the optimal regimen varies between individuals.\(^70\) Responses vary between individuals: best response is achieved in some children by adding a long-acting beta_{2} agonist, others by adding montelukast, and others by increasing the dose of inhaled corticosteroid or adding montelukast.\(^70\)

For children aged 6–14 years with persistent asthma and exercise-induced bronchoconstriction, adding montelukast is more effective in protecting against exercise-induced bronchoconstriction than switching to a combination of inhaled corticosteroid and a long-acting beta_{2} agonist.\(^71\) The use of montelukast also avoids beta-receptor tolerance associated with long-acting beta_{2} agonists, so a short-acting beta_{2} agonist taken after exercise produces a greater bronchodilator response than it does in children taking regular long-acting beta_{2} agonist.\(^71\)

Overall, adding montelukast is the best option when effects on exercise-induced symptoms and safety are also considered.\(^72\)
Managing flare-ups in adults: adjusting inhaled corticosteroid dose

Several randomised clinical trials have assessed whether increasing the inhaled corticosteroid dose is an effective strategy in avoiding the need for oral corticosteroids or acute medical care during flare-ups in adults with asthma taking daily maintenance inhaled corticosteroid or daily maintenance inhaled corticosteroid/long-acting beta2-agonist combination treatment.

There is some evidence that quadrupling the maintenance dose of inhaled corticosteroids,73 or treating with a high dose of inhaled corticosteroids,74,75,76 reduces the severity of asthma flare-ups. For patients taking inhaled corticosteroid/long-acting beta2-agonist combinations, this can be achieved by adding a separate high-dose inhaled corticosteroid inhaler to the patient’s usual maintenance treatment for 7–14 days. This strategy may be useful for patients who experience clinically important side-effects with oral corticosteroids, but may not be suitable for patients who cannot afford the extra medicine or who experience hoarseness with high dose inhaled corticosteroid. However, overall evidence from randomised clinical trials does not support the use of inhaled corticosteroids as a substitute for oral corticosteroids during most flare-ups in adults:

• A self-initiated increase (e.g. increasing the dose by a factor of two to five) after asthma worsened did not reduce the overall risk of flare-ups requiring rescue oral corticosteroids in a meta-analysis of randomised controlled clinical trials mainly in adults.77
• Doubling the dose in response to specific criteria for worsening lung function (with or without worsening asthma symptoms) did not reduce the proportion of people who needed oral corticosteroids.78 However, in two of the three clinical trials that evaluated the efficacy of doubling the dose, patients did not begin taking the higher dose (active or placebo) until approximately one week after asthma began to worsen. Therefore, there is insufficient evidence to judge the effectiveness of doubling the dose of inhaled corticosteroid at the first sign of worsening symptoms.
• In another clinical trial,73 patients taking a range of inhaled corticosteroid-based regimens at baseline were randomised to one of two treatment strategies when any of the following occurred: when peak expiratory flow rate fell (by 15% or more on 2 consecutive days, or by 30% or more on 1 day), when they believed their asthma was worsening, or they developed a cold. Treatment strategies were (1) increasing the dose of inhaled corticosteroid to four times higher than the maintenance dose, regardless of baseline regimen, or (2) continuing usual dose. Overall, the group randomised to the increased dose strategy did not have a reduced risk of flare-ups that required oral corticosteroid treatment.73 However, fewer than one quarter of patients started the study inhaler. Among those patients who did begin taking the high-dose (or placebo) inhaler due to perceived worsening asthma, quadrupling the dose was associated with a significant (almost halving) reduction in the rate of severe flare-up.73

References


Guide to preventers: inhaled corticosteroid/long-acting beta-2 agonist combinations

Preventers are used in maintenance treatment to reduce airway inflammation. They include combination inhaled corticosteroid/long-acting beta_2_ agonist medicines (budesonide/formoterol, fluticasone furoate/vilanterol, fluticasone propionate/formoterol and fluticasone propionate salmeterol).

**Table. Classification of asthma medicines**
Please view and print this figure separately: https://www.asthmahandbook.org.au/table/show/79

More information

**Inhaled corticosteroid/long-acting beta-2 agonist combinations for children: 0–5 years**

The combination of salmeterol plus fluticasone propionate in a single inhaler is registered for use in children 4 years and older. The use of long-acting beta_2_ agonists in combination with inhaled corticosteroids has not been studied in children under 4 years old. Australian and international guidelines recommend against the use of long-acting beta_2_ agonists in children aged 5 years or less.

In children aged 5 years or less with asthma that is not adequately controlled by low-dose inhaled corticosteroid alone, adding montelukast is preferable to adding a long-acting beta_2_ agonist or increasing the dose of inhaled corticosteroids when the safety profiles of these options are compared.

**Inhaled corticosteroid/long-acting beta-2 agonist combinations for children: 6 years and over**

Available combinations

Three combinations of inhaled corticosteroid and long-acting beta_2_ agonist in a single inhaler are currently available:

- The combination of fluticasone propionate and salmeterol xinafoate in a single inhaler is registered for use in children aged 4 years and over.
- The combination of budesonide and formoterol in a single inhaler is registered for use in children aged 12 years and older.
- The combination of fluticasone propionate and formoterol in a single inhaler is TGA-registered for use in children aged 12 years and older.

Role of combination therapy in children

Evidence from clinical trials does not support the use of combination therapy with a long-acting beta_2_ agonist plus an inhaled corticosteroid as initial preventer treatment in children who are not already taking inhaled corticosteroids.

Combination therapy is a step-up option for some children whose asthma is not well controlled by low-dose inhaled corticosteroids alone.

**Beta_2_ receptor regulation**

Clinical response to long-acting beta_2_ agonists partly depends on genetics. A beta_2_ receptor genotype (Arg16 polymorphism in the beta_2_ receptor gene) pre-disposes children with asthma to down-regulation of the beta_2_ receptor and increased susceptibility to flare-ups during regular treatment with long-acting beta_2_ agonists. However, routine genetic testing to tailor asthma therapy is not yet available in clinical practice.

Systematic reviews and meta-analyses have led to concern about the possibility that the use of long-acting beta-agonists (even in combination with inhaled corticosteroids) might even increase the risk of flare-ups that require treatment with oral steroids or hospital admission, or of severe flare-ups. A meta-analysis by the US Food and Drug Administration found that the use of long-acting beta_2_ agonists was associated with increased risk of severe asthma-associated adverse
events (both overall and among the subset of people using concomitant inhaled corticosteroid and long-acting beta₂ agonist), and that this risk was greatest in children aged 4–11 years.¹¹

**Inhaled corticosteroid/long-acting beta-2 agonist combinations for adults: overview**

- To avoid the possibility of patients taking a long-acting beta₂ agonist without an inhaled corticosteroid, long-acting beta₂ agonists should (whenever possible) be prescribed as inhaled corticosteroid/long-acting beta₂ agonist combination in a single inhaler, rather than in separate inhalers. If no combination product is available for the desired medications, carefully explain to the patient that it is very important that they continue taking the inhaled corticosteroid.

Meta-analysis of evidence from randomised controlled clinical trials shows that, for adult patients already taking an inhaled corticosteroid, concomitant treatment with an inhaled corticosteroid and a long-acting beta₂ agonist:¹²

- reduces the risk of flare-ups, compared with increasing the dose of corticosteroids
- reduces the risk of flare-ups, compared with inhaled corticosteroids alone.

The studies included in this meta-analysis evaluated mainly budesonide/formoterol and fluticasone propionate/salmeterol.¹²

Each of the following inhaled corticosteroid/long-acting beta₂ agonist combinations is available as a single inhaler:

- budesonide/formoterol
- fluticasone furoate/vilanterol
- fluticasone propionate/salmeterol
- fluticasone propionate/formoterol.

There are two types of dosing regimens for inhaled corticosteroid/long-acting beta₂ agonist combination therapy:

- maintenance-only regimens (applicable to all available combinations)
- maintenance-and-reliever regimen (applicable only to the budesonide/formoterol combination).

**Maintenance-only regimens**

The fluticasone propionate/salmeterol combination and budesonide/formoterol combination appear to be equally effective when used for regular maintenance treatment, based on meta-analysis of evidence from clinical trials.¹³ Most of the evidence for inhaled corticosteroid/long-acting beta₂ agonist combination therapy is from studies using these combinations.

Less evidence from double-blind randomised controlled clinical trials is available for the newer combinations: fluticasone furoate/vilanterol and fluticasone propionate/formoterol:

- The fluticasone furoate/vilanterol combination is equivalent to a medium-to-high dose of inhaled corticosteroids.¹⁴ In adults and adolescents already taking inhaled corticosteroids, once-daily fluticasone furoate/vilanterol 100/25 mcg reduced the risk of severe flare-ups (requiring oral corticosteroids or hospitalisation) and improved lung function, compared with fluticasone furoate alone.¹⁵ Efficacy data for the comparison of fluticasone furoate/vilanterol with other inhaled corticosteroid/long-acting beta₂ agonist combinations is not available.
- In adults and adolescents with persistent asthma and FEV₁ 50–80% at baseline, fluticasone propionate/formoterol achieved improvement in FEV₁ comparable to that achieved with budesonide/formoterol in a 12-week randomised double-blind clinical trial.¹⁶ Other 12-week open-label studies have reported that fluticasone propionate/formoterol was as effective as budesonide/formoterol in improving lung function in adults and adolescents with poorly controlled asthma,¹⁷ and was as effective as fluticasone propionate/salmeterol in adults.¹⁸

Long-acting beta₂ agonists should not be used without inhaled corticosteroids in the management of asthma.¹⁹,²⁰,²¹,²² Long-acting beta₂ agonists are well tolerated when given in combination with inhaled corticosteroids.¹³,²³

**Maintenance-and-reliever regimen**

The low-dose budesonide/formoterol combination can be used as both maintenance and reliever. Under this regimen, the combination is used for relief of asthma symptoms (instead of using a short-acting beta₂ agonist reliever), in addition to its use as regular maintenance treatment.

**Inhaled corticosteroid/long-acting beta-2 agonist combinations for exercise-induced bronchoconstriction**
To avoid the possibility of patients taking a long-acting beta₂ agonist without an inhaled corticosteroid, long-acting beta₂ agonists should (whenever possible) be prescribed as inhaled corticosteroid/long-acting beta₂ agonist combination in a single inhaler, rather than in separate inhalers. If no combination product is available for the desired medications, carefully explain to the patient that it is very important that they continue taking the inhaled corticosteroid.

Intermittent long-acting beta₂ agonists administered by inhalation before exercise are effective in protecting against exercise-induced bronchoconstriction:²⁴

- for formoterol, onset of bronchodilation and bronchoprotective action is 1-3 minutes after administration²⁵
- for salmeterol, onset of bronchodilation and bronchoprotective action is 10 - 30 minutes after administration²⁶

The duration of effect of both formoterol and salmeterol is up to 12 hours for patients who have not taken a short-acting beta₂ agonist or long-acting beta₂ agonist within the previous 72 hours. However, the duration of bronchoprotection is reduced for subsequent doses due to receptor tolerance.²⁴

**Combination budesonide/formoterol maintenance-and-reliever regimen in adults and adolescents: overview of efficacy**

Low-dose budesonide/formoterol combination can be used as reliever for asthma symptoms (instead of using a short-acting beta₂ agonist reliever), in addition to its use as regular long-term preventer treatment.²⁷ 6, 28, 29, 30, 31 The following formulations can be used in maintenance-and-reliever regimens:

- dry-powder inhaler (*Symbicort Turbuhaler*) 100/6 mcg or 200/6 mcg
- pressurised metered-dose inhaler (*Symbicort Rapihaler*) 50/3 mcg or 100/3 mcg.

Neither the 400/12 mcg dry-powder inhaler nor the 200/6 mcg pressurised metered-dose inhaler should be used in this way.

Overall, clinical trials show that budesonide/formoterol combination as maintenance and reliever reduces the risk of flare-ups that require oral corticosteroids, compared with other current preventer regimens and compared with a fixed higher dose of inhaled corticosteroids.³²

Pooled data from five randomised controlled trials assessing budesonide/formoterol maintenance-and-reliever regimens showed that similar or better levels of asthma control were achieved with budesonide/formoterol maintenance-and-reliever compared with the conventional maintenance regimen comparators:²⁸

- higher-dose budesonide
- same dose budesonide/formoterol
- higher-dose inhaled corticosteroid/long-acting beta₂ agonist (budesonide/formoterol or fluticasone propionate/salmeterol).

In randomised clinical trials in patients with a history of asthma flare-up within the previous 12 months (and therefore at greater risk of flare-up in the next 12 months), the use of formoterol/budesonide as maintenance-and-reliever regimen reduced the risk of asthma flare-ups that required treatment with oral corticosteroids, compared with the use of any of the following (plus a short-acting beta₂ agonist reliever as needed):²⁸ 33, 34

- the same combination as maintenance treatment only
- higher-dose combination as maintenance treatment only
- higher-dose inhaled corticosteroids.

Meta-analysis of six randomised controlled trials found that maintenance-and-reliever treatment with budesonide/formoterol reduced the risk of severe asthma flare-ups (use of oral corticosteroids for 3 days or more, hospitalisation or emergency department visits), compared with higher-dose inhaled corticosteroid alone, or in combination with a long-acting beta₂ agonist.³⁵

In open-label studies in which patients were not selected for a previous history of flare-ups, there was no overall difference in time to first flare-up between budesonide/formoterol as maintenance-and-reliever regimen and conventional maintenance regimens (including inhaled corticosteroid or inhaled corticosteroid/long-acting beta₂ agonist combinations, leukotriene receptor antagonists, xanthines or any other asthma medicines) with rapid-onset beta₂ agonist reliever (selected according to clinician’s choice).³⁶ However, the inhaled corticosteroid dose was higher with conventional maintenance regimens.

**Note:** The fluticasone propionate/formoterol combination is approved by the Therapeutic Goods Administration only for regular maintenance therapy.
Managing flare-ups in adults: adjusting budesonide/formoterol maintenance-and-reliever treatment

When asthma symptoms worsen, patients taking budesonide/formoterol 100/6 mcg or 200/6 mcg as maintenance-and-reliever treatment can increase as-needed inhalations:

- for budesonide/formoterol 100/6 mcg or 200/6 mcg via dry-powder inhaler, up to a maximum of 12 actuations per day (total of maintenance and reliever inhalations) 6
- for budesonide/formoterol 50/3 mcg or 100/3 mcg via pressurised metered-dose inhaler, up to a maximum of 24 actuations per day (total of maintenance and reliever inhalations).37

A written asthma action plan template developed by Australian clinicians for adults using budesonide/formoterol maintenance and reliever regimen suggests that the patient should commence oral corticosteroids and/or see a doctor after 2–3 days if asthma is worsening, or symptoms are not improving, despite taking 6 reliever inhalations of budesonide/formoterol per day in addition to maintenance doses.

▶ Go to: National Asthma Council Australia’s written asthma action plan for adults using budesonide/formoterol maintenance and reliever regimen in the Asthma Action Plan Library

References

Guide to preventers: montelukast

Overview

Preventers are used in maintenance treatment to reduce airway inflammation. They include leukotriene receptor antagonists (montelukast).

Table: Classification of asthma medicines
Please view and print this figure separately: https://www.asthmahandbook.org.au/table/show/79

More information

Montelukast for adults: efficacy

In adults and adolescents with asthma that is not controlled by low-dose inhaled corticosteroid, the addition of a leukotriene receptor antagonist is less effective than the addition of a long-acting beta_2_ agonist in reducing the rate of asthma flare-ups that require treatment with oral corticosteroids. The addition of a leukotriene receptor antagonist is also associated with lesser improvement in lung function and quality of life than the addition of a long-acting beta_2_ agonist.

Montelukast taken 1 hour before exercise can be used to manage exercise-induced bronchoconstriction, but it is less effective than short-acting beta_2_ agonists.

Retrospective analysis of clinical trial data suggests that some people with asthma who smoke, or are obese, may achieve better asthma control with montelukast than an inhaled corticosteroid. However, prospective studies would be needed to confirm this.

Some individuals may also achieve better asthma control with montelukast than with an inhaled corticosteroid for reasons that are unknown and cannot be predicted from currently available data.

Although montelukast was previously thought to have particular benefits for people with aspirin-intolerant asthma, this has not been consistently demonstrated in clinical trials.

Within specialised severe asthma clinics, montelukast is sometimes prescribed as add-on treatment for adults.

Note: PBS status as at October 2016: Montelukast treatment is not subsidised by the PBS for people aged 15 years or over. Special Authority is available for DVA gold card holders or white card holders with approval for asthma treatments.

Montelukast for adults and adolescents: psychiatric effects

Post-marketing surveillance reports led to concerns about a possible association between leukotriene receptor antagonist use and suicide risk. A recent case-control study reported a statistically significant association between the use of leukotriene receptor antagonists and suicide attempts in people aged 19–24 years. However, this association was no longer statistically significant after adjusting for potential confounding factors, including previous exposure to other asthma medicines and previous exposure to other medicines associated with suicide.

Montelukast for children

Montelukast is registered by the TGA for use in children aged 2 years and older.

Based on data from placebo-controlled trials, it has not been possible to define clinical indicators that predict which children will benefit most from montelukast therapy, compared with other treatment options.
Comparative studies suggest that the main role for montelukast is as an alternative to low-dose inhaled corticosteroid in children with frequent intermittent asthma or mild persistent asthma.\textsuperscript{7}

**Children 0–5 years**

In preschool children with multiple-trigger wheeze, montelukast protects against airway hyperresponsiveness when taken with or without inhaled corticosteroids.\textsuperscript{8} Inhaled corticosteroids are more effective than montelukast in children with multiple-trigger wheeze aged 2–8 years,\textsuperscript{9} but this comparison has not been made in preschool children as a separate group.\textsuperscript{8}

In children aged 2–5 years with episodic (viral) wheeze, regular montelukast treatment reduces the risk of wheezing episodes.\textsuperscript{10} However, montelukast may not reduce symptoms in children aged 6–24 months with recurrent wheeze.\textsuperscript{11}

**Note:** Montelukast is not TGA-registered for use in children younger than 2 years.

A short course of montelukast, introduced at the first signs of an asthma episode or upper respiratory tract infection, can achieve a small reduction in symptoms, school absence and medical consultations in preschool and school-aged children with episodic wheeze.\textsuperscript{12} However, montelukast is not TGA-registered for intermittent use.

**Children 6 years and over**

In school-aged children with persistent asthma, inhaled corticosteroids are more effective than montelukast for a range of measures, including lung function.\textsuperscript{7}

In school-aged children with persistent exercise-induced symptoms despite taking regular inhaled corticosteroids, montelukast is effective in controlling symptoms and is more effective than long-acting beta\textsubscript{2} agonists.\textsuperscript{13, 14}

In children who are already taking regular inhaled corticosteroids and have a beta\textsubscript{2} receptor genotype associated with increased susceptibility to flare-ups during regular long-acting beta\textsubscript{2} agonist therapy,\textsuperscript{15} montelukast may be more effective than salmeterol in reducing symptoms, reliever use and days absent from school due to asthma, based on the findings of a small randomised controlled clinical trial.\textsuperscript{15}

Go to: National Asthma Council Australia’s [Leukotriene receptor antagonists in the management of childhood asthma](http://www.nationalasthma.org.au/resources/leukotriene-receptor-antagonists-in-the-management-of-childhood-asthma/)

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**Montelukast for children: warning parents about potential psychiatric adverse effects**

Montelukast is generally very well tolerated.\textsuperscript{13} However, post-marketing surveillance reports suggested a slight increase in the rate of psychiatric disorders that was possibly associated with use of leukotriene receptor antagonists in children;\textsuperscript{16} this association may have been confounded by asthma severity and concomitant medication.\textsuperscript{12} Montelukast use has also been associated with suicidal ideation, but a recent nested case-control study concluded that children with asthma aged 5 –18 years taking leukotriene receptor antagonists were not at increased risk of suicide attempts.\textsuperscript{3} Behavioural and psychiatric adverse effects were rare in clinical trials.\textsuperscript{17, 18}

The Thoracic Society of Australia and New Zealand advises that it is prudent to mention to parents the potential association of montelukast with behaviour-related adverse events when commencing treatment, and to cease therapy if such adverse events are suspected.\textsuperscript{13}

Go to: [TGA’s safety update on montelukast and neuropsychiatric risks](http://www.tga.gov.au/safety-update-montelukast-neuropsychiatric-risk)

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**Montelukast for exercise-induced bronchoconstriction**

Montelukast is less effective against exercise-induced bronchoconstriction than short-acting beta\textsubscript{2} agonists, but regular use is not associated with receptor tolerance.\textsuperscript{2}

Montelukast taken either intermittently before exercise or daily is at least partially effective in protecting against exercise-induced bronchoconstriction in some, but not all patients.\textsuperscript{2} Some experience strong protection against exercise-induced bronchoconstriction while others experience only partial protection or no effect.\textsuperscript{2} Very few patients experience complete protection against exercise-induced bronchoconstriction.\textsuperscript{2}

In children, regular montelukast, either as the child’s only preventer or in combination with an inhaled corticosteroid, is more effective than long-acting beta\textsubscript{2} agonists in protecting against exercise-induced bronchoconstriction,\textsuperscript{14, 19} and is associated with a greater bronchodilator response to short-acting beta\textsubscript{2} agonist after exercise.\textsuperscript{14}
The onset of protection occurs within 2 hours of dosing. The duration of protective effect is 12–24 hours. Recommended doses are as follows:

- children aged 2–5 years 4 mg daily, or 1–2 hours before exercise
- children aged 6–14 years 5 mg daily, or 1–2 hours before exercise
- adults 10 mg daily, or 1–2 hours before exercise.

Notes

PBS status as at October 2016: Montelukast treatment is not subsidised by the PBS for:

- people aged 15 years or over (Special Authority is available for DVA gold card holders, or white card holders with approval for asthma treatments.)
- children aged 2 to 5 years in combination with any other preventer
- children aged 6 to 14 years with moderate to severe asthma, when used use as a single second-line preventer as an alternative to corticosteroids
- people of any age, when used in addition to a long-acting beta-agonist.

Oral montelukast in acute asthma

Evidence from randomised controlled clinical trials does not support routine use of oral leukotriene receptor agonists in acute asthma in adults or children. In children with acute asthma, the addition of oral montelukast to usual care does not reduce hospital admission rates, based on the findings of a systematic review and meta-analysis. In adults with acute asthma, the addition of oral montelukast to usual care may slightly reduce beta2 agonist requirement. The addition of oral zafirlukast was associated with improvement in lung function, compared with usual care.

References


Guide to preventers: cromones

Overview

Preventers are used in maintenance treatment to reduce airway inflammation. They include cromones (cromoglycate and nedocromil sodium).

Table. Classification of asthma medicines
Please view and print this figure separately: https://www.asthmahandbook.org.au/table/show/79

More information

Cromones for children

0-5 years
Few clinical trials have assessed the use of inhaled sodium cromoglycate in preschool children and none have assessed nedocromil. Overall, sodium cromoglycate has not been shown to be effective in preschool children with multiple-trigger wheeze. However, cromones are well tolerated and registered for use in infants. Therefore, a treatment trial can be considered before considering other preventers, particularly for children less than 2 years old.

6 years and over
Cromones are rarely prescribed in school-aged children. Inhaled sodium cromoglycate might be effective in school-aged children, but interpretations of available evidence are inconsistent. Sodium cromoglycate is less effective than inhaled corticosteroid in achieving asthma control and improving lung function in children with persistent asthma. Nedocromil sodium appears to be have some benefit in children with persistent asthma, but its relative effectiveness compared with inhaled corticosteroids is not clear. Long-term (4–6 years) treatment with budesonide achieved better asthma control than long-term nedocromil in children with mild-to-moderate asthma aged 5–12 in a randomised placebo-controlled clinical trial.

Practical issues
Cromones (sodium cromoglycate and nedocromil) may not be practical for some patients, because they require three–four times daily dosing until control is gained, and inhaler devices for cromones tend to block easily. Nedocromil can cause an unusual or unpleasant taste and is not tolerated by some children.

Cromones for adults and adolescents
Sodium cromoglycate is less effective than inhaled corticosteroids in controlling asthma and improving lung function. Cromolyn sodium and nedocromil sodium taken before exercise can be used to manage exercise-induced bronchoconstriction, but they are only effective in approximately 50% of patients and are less effective than short-acting beta₂ agonists. Cromones have a good safety profile and tolerance does not occur when either of these medicines is taken regularly. Maintenance of the CFC-free device is difficult for patients because the formulation is sticky and blocks the device unless it is washed and thoroughly dried every day. Therefore, patients need two mouthpieces to use alternately.

► See: Investigation and management of exercise-induced bronchoconstriction
Cromolyn sodium and nedocromil sodium administered by inhalation as single doses before exercise partially protect against exercise-induced bronchoconstriction in approximately half of patients. The onset of action is rapid. The duration of action is up to 2 hours.

Recommended doses are as follows:
- nedocromil sodium 4–8 mg by inhalation, 5–10 minutes before exercise
- sodium cromoglycate 10–20 mg by inhalation, 5–10 minutes before exercise.

Cromolyn sodium and nedocromil sodium are less effective than short-acting beta₂ agonists in protecting against exercise-induced bronchoconstriction. However, they have a good safety profile and tolerance does not occur when either of these medicines is taken regularly.

Sodium cromoglycate and nedocromil sodium inhalers must be washed daily to prevent blockage.

References

Guide to systemic corticosteroids

Overview

Short courses of systemic corticosteroids are used to manage flare-ups and acute asthma. Oral prednisone/prednisolone is most commonly used. Parenteral corticosteroids are sometimes used to manage severe acute asthma in emergency departments.

Occasionally, longer-term use of oral corticosteroids is necessary to manage difficult-to-treat asthma under specialist supervision.

Table. Classification of asthma medicines

Please view and print this figure separately: https://www.asthmahandbook.org.au/table/show/79

More information

Oral corticosteroids for children: 0–5 years

Few clinical trials have assessed the effectiveness of oral corticosteroids for managing flare-ups of wheezing in preschool children, and there is very little evidence about their effects in children who are not being treated in hospitals or emergency departments.

Short courses of oral corticosteroids initiated by parents in response to the onset of wheezing symptoms do not appear to reduce the need for hospitalisation or treatment in the emergency department for preschool children. For children age 1–5 years with wheezing due to a respiratory tract virus such as the common cold, a short course of oral prednisolone does not reduce the severity of symptoms.

Oral corticosteroids for children: 6 years and over

A short course of oral corticosteroid may be helpful in gaining rapid asthma control, with a low risk of additional systemic adverse effects.

Rarely, long-term systemic corticosteroids may be needed for children with severe persistent asthma that is poorly controlled despite high-dose inhaled corticosteroids and long-acting beta2 agonists. However, significant adverse effects may occur due to recurrent or long-term systemic corticosteroids.

Oral corticosteroids for children: adverse effects

A short course of oral corticosteroid therapy (less than 2 weeks) is associated with little risk of long-term suppression of the hypothalamus–pituitary–adrenal axis. However, risk can accumulate if frequent courses (four or more per year) are given.

Recurrent courses of oral corticosteroids may also affect bone mineral density, especially in boys.

Parent-initiated oral corticosteroid treatment in children

There is limited and inconclusive evidence from clinical trials evaluating the effectiveness of courses of oral corticosteroids initiated by parents in response to children’s wheezing.

In children aged 6–14 years, a course of oral prednisolone initiated by parents in response to an asthma flare-up may reduce asthma symptoms and the number of missed school days.
In children aged 1–5 years with episodic wheezing, oral corticosteroids are not effective in managing the symptoms of acute lower respiratory tract illnesses.\(^7\)

**Managing flare-ups in adults: oral corticosteroids**

The use of oral corticosteroids is accepted as part of the management of severe asthma flare-ups, including in most asthma clinical trials.

Most clinical trials that have specifically evaluated the use of oral corticosteroids to manage flare-ups have been conducted in patients attending emergency departments. Oral corticosteroids courses of 5–10 days are effective in regaining control of asthma after an acute flare-up.\(^8, 9, 10, 11, 12\) A 5-day course of prednisolone 40 mg per day may be as effective as a 10-day course in adults.\(^10\)

Abruptly ceasing oral prednisolone after a short course appears to be equally effective as tapering over a longer period. Tapering the dose does not reduce the risk of suppression of adrenal function.\(^8, 11\) The dose should be tapered if oral corticosteroids have been taken for more than 2 weeks.

Action plans for worsening asthma that include instructions for the use of oral corticosteroids as well as instructions to increase the dose of inhaled corticosteroid, are effective in improving lung function and reducing hospital admissions.\(^13\)

**Systemic corticosteroids in acute asthma**

Systemic corticosteroids given within 1 hour of presentation to an emergency department reduce the need for hospital admission in patients with acute asthma, particularly if they have severe asthma or are not already taking systemic corticosteroids.\(^14\)

Oral prednisolone is as effective as intravenous or intramuscular corticosteroids during acute asthma in adults.\(^15, 16, 17\) Doses of up to 80 mg/day methylprednisolone (or up to 400 mg/day hydrocortisone) are adequate. Higher doses do not appear to be more effective in adults with acute asthma.\(^18\)

After an acute asthma episode, a short course of systemic corticosteroids reduces the risk of relapse, hospitalisations, and use of short-acting beta\(_2\)-agonist, and appears to be well tolerated.\(^12\) Oral and intramuscular corticosteroids are both effective.\(^12\)

A course of 5–10 days is sufficient.\(^8, 9, 11\) In adults, a 5-day course of prednisolone 40 mg per day may be as effective as a 10-day course.\(^10\) In children, a 3-day course is generally effective, but 5 days may be needed for children with severe or life-threatening acute asthma.\(^4\) The majority of studies have used 2mg/kg of oral prednisolone (maximum 60 mg) given initially then 1mg/kg per day.

Abruptly ceasing a short (less than 2 weeks) course of oral prednisolone appears to be equally effective as tapering the dose, and does not suppress adrenal function.\(^8, 11\)

**Note:** The recommendation in this Handbook for a maximum prednisolone dose of 50 mg for children is based on practical considerations, taking into account commercially available doses and strengths and consistency with the dose recommended for adults.

**Systemic corticosteroids in acute asthma: adverse effects**

Short-term use of oral corticosteroids is unlikely to cause harm – the majority of adverse effects are due to long-term high-dose use.\(^19\) Adverse effects associated with prednisone or prednisolone use include headache, nausea, vomiting, increased appetite, diarrhoea or constipation, vertigo, restlessness, insomnia and increased activity, salt and water retention, and increased blood pressure. High doses can be associated with behavioural changes, facial plethora, bruising and increased sweating.\(^19\)

In people with diabetes or impaired glucose tolerance, corticosteroids increase blood glucose levels. Impaired glucose tolerance is common among people aged over 65 years. In patients with diabetes or impaired glucose tolerance, blood glucose monitoring (e.g. morning and evening samples) may be indicated during treatment with oral corticosteroids.

Long-term use of oral corticosteroids increases the risk of cataracts and osteoporosis in older patients,\(^20\) and may increase body weight.

**Systemic corticosteroids: psychiatric effects**

Systemic corticosteroids can have a range of psychological effects. Large doses of prednisone or prednisolone can cause mood and behavioural changes, including nervousness, euphoria or mood swings, psychotic episodes including manic or
depressive states, paranoid states and acute toxic psychoses.\textsuperscript{19} These adverse effects can occur in people without a previous history of psychiatric illness.\textsuperscript{19}

Systemic corticosteroid treatment has been associated with elevated mood and reduction in depression among patients with asthma.\textsuperscript{21, 22} With long-term prednisone or prednisolone therapy, initial mood changes appear to stabilise over time.\textsuperscript{23}

**Systemic corticosteroids and breast milk**

Peak plasma level of systemic corticosteroid occurs at approximately 2 hours post dose, so peak milk level will also occur around this time. Therefore, the infant’s exposure to corticosteroids in breast milk can be further reduced by breastfeeding the infant just before each daily dose and avoiding feeding again until at least 4 hours after the dose.\textsuperscript{24, 25}

If high-dose corticosteroids need to be used for longer than 10 days, the infant should be monitored for growth and development.\textsuperscript{24, 25}

The US National Library of Medicine’s Drugs and Lactation Database (LactMed) states that: limited information indicates that maternal doses of prednisolone up to 50 mg produce low levels in milk and would not be expected to cause any adverse effects in breastfed infants. With high maternal doses, avoiding breastfeeding for 4 hours after a dose should markedly decrease the dose received by the infant. However, this [manoeuvre] is probably not necessary in most cases.

Go to: The US National Library of Medicine's Drugs and Lactation Database (LactMed)

References


Guide to other asthma medicines

Overview

In addition to relievers and preventers, some other agents are occasionally used to manage asthma in specific circumstances, e.g. as add-on options for management of severe refractory asthma, co-existing COPD and asthma, or severe acute asthma. They include:

- anti-IgE (omalizumab)
- anti-IL5 (mepolizumab)
- long-acting muscarinic antagonists; also called long-acting anticholinergic bronchodilators (aclidinium, glycopyrronium, tiotropium, umeclidinium)
- magnesium sulfate
- theophyllines (aminophylline, theophylline).

Table. Classification of asthma medicines

Please view and print this figure separately: https://www.asthmahandbook.org.au/table/show/79

More information

Omalizumab

Omalizumab is a treatment option for some adults and children aged 6 years and over with difficult-to-treat asthma.\(^1\,^2\)

It is approved by the Therapeutic Goods Administration for use in:\(^3\)

- adults and adolescents aged 12 years and over with moderate-to-severe allergic asthma that is not controlled while taking inhaled corticosteroid and who have raised IgE levels.
- children aged 6 to 11 years with severe allergic asthma who have documented exacerbations despite daily high-dose inhaled corticosteroids and who have raised IgE levels.

When given in addition to inhaled corticosteroids, omalizumab is effective in helping control asthma in patients with severe asthma, particularly those with asthma that is not controlled despite regular treatment with inhaled corticosteroid at medium-to-high dose plus long-acting beta\(_2\) agonist, with or without other add-on treatments.\(^1\) Clinical trials have shown that omalizumab reduces the rate of asthma flare-ups, enables a reduction in inhaled corticosteroid dose, improves symptoms, reduces short-acting beta\(_2\) agonist reliever requirement, improves quality of life and achieves a small increase in FEV\(_1\).\(^1\)

Omalizumab treatment is generally well tolerated, but is associated with injection site reactions.\(^4\) It has been associated with anaphylactoid reactions, which can occur more than 2 hours after injection,\(^1\) so patients must carry adrenalin for self-administration (e.g. EpiPen) at all times. Early reports suggested that omalizumab may be associated with an increased risk of malignancy.\(^1\) However, subsequent pooled results indicate that a causal relationship between omalizumab therapy and malignancy is unlikely.\(^5\)

Note: Omalizumab treatment in adults and adolescents is subsidised through the PBS for use in patients with severe allergic asthma who meet certain criteria, including monitoring for at least 12 months by a specialist (respiratory physician, clinical immunologist, allergist or general physician) experienced in the management of patients with severe asthma. PBS criteria for continuation of treatment include demonstration of a therapeutic response by recording asthma symptom control, at baseline and after 6 months of treatment, using the 5-item Asthma Control Questionnaire (ACQ-5).

As at October 2016, omalizumab treatment is not subsidised by the PBS for children aged 6 to 11 years.

Go to: Thoracic Society of Australia and New Zealand’s Omalizumab (Xolair): Recommendations for use in the Australasian context
Go to: International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma
**Ipratropium for children**
Cochrane systematic reviews concluded that, overall, clinical trial evidence does not support the regular use of muscarinic antagonists (anticholinergic bronchodilators) in the maintenance treatment of asthma in children (i.e. outside the context of acute asthma). 

►See: Managing acute asthma in clinical settings

**Ipratropium for adults**
Regular ipratropium bromide in addition to as-needed short-acting beta\(_2\) agonist does not appear to provide clinically significant benefit over as-needed short-acting beta\(_2\) agonists alone.

Note: Ipratropium bromide may be used in the management of severe acute asthma.

►See: Managing acute asthma in clinical settings

**Tiotropium for adults**
A meta-analysis of 13 randomised placebo-controlled clinical trials in patients with asthma found that tiotropium as an add-on in patients taking inhaled corticosteroids improved lung function, reduced the rate of flare-ups, and improved asthma symptom control. In patients with poorly controlled asthma despite treatment with medium-to-high doses of inhaled corticosteroids, tiotropium was not inferior to salmeterol.

In patients taking a combination of an inhaled corticosteroid and salmeterol, the addition of tiotropium increased lung function, reduced the rate of flare-ups, and improved asthma symptom control.

Tiotropium was well tolerated.

A Cochrane review that included five double-blind, double-dummy trials found that the addition of tiotropium to inhaled corticosteroid therapy reduced the risk of flare-ups requiring systemic corticosteroids and improved lung function, compared with the same dose of inhaled corticosteroid, in adults not taking a long-acting beta\(_2\) agonist.

Another Cochrane review concluded that tiotropium in addition to the combination of an inhaled corticosteroid and a long-acting beta\(_2\) agonist may have additional benefits over inhaled corticosteroid/long-acting beta\(_2\) agonist alone in reducing the need for rescue oral corticosteroids in adults with severe asthma.

**Ipratropium in acute asthma**
Ipratropium bromide alone is less effective than salbutamol alone in acute asthma.

Early administration of ipratropium bromide in addition to beta\(_2\) agonists may reduce admission rates and improve lung function in children and adults with acute asthma, based on the findings of a systematic review of 32 randomised controlled trials.

However, ipratropium bromide does not appear to benefit patients with less severe acute asthma (patients with acute asthma assessed as ‘mild’ in randomised controlled trials, e.g. FEV\(_1\) >70% predicted).

Ipratropium bromide may be effective in patients with tolerance to the bronchodilator effect of short-acting beta-agonists caused by beta-receptor down-regulation.

It is well tolerated in children with acute asthma.

**Magnesium sulfate in acute asthma**

MgSO\(_4\) versus beta\(_2\) agonists
Clinical trial evidence does not support the use of magnesium sulfate as a substitute for inhaled beta\(_2\) agonists.

Intravenous MgSO\(_4\) plus beta\(_2\) agonist
In patients with life-threatening acute asthma (FEV₁ 25–30% predicted) or patients with a poor response to initial bronchodilator treatment, intravenous magnesium sulfate (2 g given as a single infusion over 20 minutes) can reduce hospital admission rates. However, it may only be effective in patients with more severe acute asthma. In a recent large, well-conducted randomised controlled trial in adults with moderate-to-severe acute asthma treated in an emergency department (excluding those with life-threatening asthma), intravenous magnesium sulfate improved dyspnoea scores but did not reduce hospital admission rates.

In children, intravenous magnesium sulfate improves lung function and reduces the need for hospital admission. Fewer studies have been conducted in children under 6 years.

Intravenous magnesium sulfate is inexpensive and generally well tolerated.

**Inhaled MgSO₄ plus beta₂ agonist**

Overall, evidence from randomised controlled clinical trials suggests that nebulised magnesium sulfate in addition to beta₂ agonist (with or without ipratropium bromide) does not reduce hospital admissions or improve lung function in adults or children, compared with beta₂ agonist alone. However, the results of some clinical trials suggest that the addition of nebulised magnesium sulfate improves lung function in patients with severe acute asthma (FEV₁ <50% predicted). In a recent large randomised controlled clinical trial in children, nebulised magnesium sulfate was associated with a small improvement in asthma symptom scores at 60 minutes. The effect was greatest in the subgroups of children with more severe acute asthma, and those with a shorter duration of symptoms. A recent study showed no benefit in adults for hospitalisation or dyspnoea with add-on nebulised magnesium compared with standard therapy alone, but this study excluded patients with life-threatening acute asthma as defined in this handbook.

Fewer studies have been conducted in children than in adults.

**Theophyllines in acute asthma**

**Aminophylline versus short-acting beta₂ agonist**

Intravenous aminophylline may be as effective as intravenous short-acting beta₂ agonist in the management of acute asthma in adults and children, but is associated with a higher rate of adverse effects including giddiness, nausea and vomiting.

**Aminophylline plus beta₂ agonist (adults)**

Overall, evidence from randomised clinical trials in adults with acute asthma treated in emergency departments suggests that intravenous aminophylline given in addition to inhaled beta₂ agonists does not achieve greater bronchodilation or reduce hospital admissions, compared with inhaled beta₂ agonists alone. No sub-groups that benefit from intravenous aminophylline have been clearly identified. Aminophylline is associated with vomiting and cardiac arrhythmias. Theophylline is metabolised mainly by the liver and commonly interacts with other medicines. Its concentration in plasma should be monitored closely in older people or those with comorbid conditions.

- Avoid short-acting theophylline for a patient who is already using long-acting theophylline.

**Aminophylline plus beta₂ agonist (children)**

Overall, evidence from randomised clinical trials in children with acute asthma requiring hospital admission suggests that the addition of intravenous aminophylline to beta₂-agonists and corticosteroids, with or without muscarinic antagonists (anticholinergic bronchodilators), improves lung function within 6 hours of treatment, but does not appear to improve symptoms or shorten hospital stay. Aminophylline is associated with a significant increased risk of vomiting in children.

**References**

Guide to use of asthma medicines in sport

Overview

Many sporting bodies have restrictions regarding the use of asthma medicines during competition. Anti-doping agencies provide information about which medicines are permitted and under which circumstances.

More information

Use of medicines in sport

Many sporting bodies require athletes to provide objective evidence of exercise-induced bronchoconstriction before they are permitted to use asthma medicines during competition.

The Australian Sports Anti-Doping Authority provides information about Therapeutic Use Exemptions for athletes who require treatment with prohibited substances.

▶ Go to: Australian Sports Anti-Doping Authority
    Go to: World Anti-Doping Agency

Anti-doping agencies

Australian Sports Anti-Doping Authority
The Australian Sports Anti-Doping Authority (ASADA) is the Australian federal government statutory authority with a mission to protect Australia’s sporting integrity through the elimination of doping.

▶ Go to: ASADA or call 13 000 ASADA (13 000 27232)
    Go to: ASADA’s Check your substances webpage

World Anti-Doping Agency
The World Anti-Doping Agency (WADA) is the international independent anti-doping agency composed of representatives from the Olympic movement and public authorities from around the world. Its mission is to lead a collaborative worldwide campaign for doping-free sport.

▶ Go to: WADA