National Asthma Council Australia

AUSTRALIAN ASTHMA HANDBOOK

VERSION 2.0

# RESOURCES

*Medicines guide*

*Tools*

*Patient resources*

*Definitions*

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

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## ABBREVIATIONS

| | |
|---|---|
| **CFC** | chlorofluorocarbon |
| **COPD** | chronic obstructive pulmonary disease |
| **COX** | cyclo-oxygenase |
| **DXA** | dual-energy X-ray absorptiometry |
| **ED** | emergency department |
| **EIB** | exercise-induced bronchoconstriction |
| **$FEV_1$** | forced expiratory volume over one second |
| **$FEV_6$** | forced expiratory volume over six seconds |
| **FSANZ** | Food Standards Australia and New Zealand |
| **FVC** | forced vital capacity |
| **GORD** | gastro-oesophageal reflux disease |
| **HFA** | formulated with hydrofluroalkane propellant |
| **ICS** | inhaled corticosteroid |
| **ICU** | intensive care unit |
| **IgE** | Immunoglobulin E |
| **IL** | interleukin |
| **IU** | international units |
| **IV** | intravenous |
| **LABA** | long-acting beta$_2$-adrenergic receptor agonist |
| **LAMA** | long-acting muscarinic antagonist |
| **LTRA** | leukotriene receptor antagonist |
| **MBS** | Medical Benefits Scheme |
| **NHMRC** | National Health and Medical Research Council |
| **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 |
| **PaO** | oxygen partial pressure on blood gas analysis |
| **PBS** | Pharmaceutical Benefits Scheme |
| **PEF** | peak expiratory flow |
| **pMDI** | pressurised metered-dose inhaler or 'puffer' |
| **PPE** | personal protective equipment |
| **SABA** | short-acting beta$_2$ -adrenergic receptor agonist |
| **SAMA** | short-acting muscarinic antagonist |
| **$SaO_2$** | oxygen saturation |
| **$SpO_2$** | peripheral capillary oxygen saturation measured by pulse oximetry |
| **TGA** | Therapeutic Goods Administration |

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AUSTRALIAN ASTHMA HANDBOOK



# Resources

## In this section

*Medicines guide*

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

**http://www.asthmahandbook.org.au/resources/medicines-guide**

*Tools*

Tools and support for asthma management in primary care, including tools for assessing asthma control and links to support organisations

**http://www.asthmahandbook.org.au/resources/tools**

*Patient resources*

Tools and support that primary carers can offer to patients to improve self-management and health literacy

**http://www.asthmahandbook.org.au/resources/patients**

*Definitions*

Explanatory notes on terms used in the handbook, including a working definition of asthma, definitions of special terms, and explanations of abbreviations and technical words.

**http://www.asthmahandbook.org.au/resources/definitions**

# 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 beta$_2$ 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 beta$_2$ 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*

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

▶ Go to: National Asthma Council Australia's *Asthma and COPD Medications Chart*

## In this section

*Reliever medicines*

Guide to reliever medicines

**http://www.asthmahandbook.org.au/resources/medicines-guide/relievers**

*Preventer medicines*

Guide to preventer medicines

**http://www.asthmahandbook.org.au/resources/medicines-guide/preventers**

*Systemic corticosteroids*

Guide to systemic corticosteroids

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*Other asthma medicines*

Guide to other asthma medicines

**http://www.asthmahandbook.org.au/resources/medicines-guide/other-medicines**

*Medicines in sport*

Guide to use of asthma medicines in sport

**http://www.asthmahandbook.org.au/resources/medicines-guide/sport**

# 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.

*Table. Classification of asthma medicines*

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

## More information

### *Short-acting beta-2 agonist relievers for children: 1–5 years*

#### *Infants under 12 months*

In infants under 12 months, bronchiolitis is the most likely cause of acute respiratory distress. Bronchodilators are not recommended in children under 12 months old, consistent with current guidelines for the management of acute bronchiolitis.[1]

#### *Children aged 1–5 years*

Inhaled short-acting beta$_2$ agonists are effective bronchodilators in children aged 1–5 years.[2]

Short-acting beta$_2$ agonists may be less effective for wheezing in children under 2 years old than in older children.[3] 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.[3] 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.[3]

Inhaled short-acting beta$_2$ agonists are generally well tolerated in children aged 1–5 years.[2] Adverse effects can include muscle tremor, headache, palpitations and agitation. Muscle tremor and agitation are common with initial use of standard doses, but often settle over time. Serious adverse effects such as hypokalaemia have been reported at very high doses.[2]

Oral short-acting beta$_2$ agonists are associated with adverse effects[2] and should not be used for the treatment of asthma in any age group.

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

Inhaled short-acting beta$_2$ agonists is the major class of bronchodilators used for relief of symptoms in asthma.[4]

Children with well-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.

Dispensing of 3 or more canisters in a year (average 1.6 puffs per day) is associated with increased risk of flare-ups.[1] Dispensing 12 or more canisters in a year (average 6.6 puffs per day) is associated with increased risk of asthma death.[2]

**Table. Definition of levels of recent asthma symptom control in children (regardless of current treatment regimen)**

| Good control | Partial control | Poor control |
|---|---|---|
| All of:<br>• Daytime symptoms† ≤2 days per week (lasting only a few minutes and rapidly relieved by rapid-acting bronchodilator)<br>• No limitation of activities‡<br>• No symptoms§ during night or when wakes up<br>• Need for SABA reliever# ≤2 days per week | Any of:<br>• Daytime symptoms† >2 days per week (lasting only a few minutes and rapidly relieved by rapid-acting bronchodilator)<br>• Any limitation of activities*<br>• Any symptoms during night or when wakes up††<br>• Need for SABA reliever# >2 days per week | Either of:<br>• Daytime symptoms† >2 days per week (lasting from minutes to hours or recurring, and partially or fully relieved by SABA reliever)<br>• ≥3 features of partial control within the same week |

SABA: short-acting beta$_2$ agonist

† e.g. wheezing or breathing problems

‡ child is fully active; runs and plays without symptoms

§ including no coughing during sleep

# not including doses 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

†† e.g. waking with symptoms of wheezing or breathing problems

**Notes**:

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.

**Validated questionnaires can be used for assessing recent symptom control:**
Test for Respiratory and Asthma Control in Kids (TRACK) for children < 5 years
Childhood Asthma Control Test (C-ACT) for children aged 4–11 years

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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.[5] 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.

Dispensing of three or more canisters in a year (average 1.6 puffs per day) is associated with increased risk of flare-ups.[6] Dispensing 12 or more canisters in a year (average 6.6 puffs per day) is associated with increased risk of asthma death.[7]

**Note**: Routine preventive doses of short-acting beta$_2$ 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)**

| Good control | Partial control | Poor control |
|---|---|---|
| All of:<br>• Daytime symptoms ≤2 days per week<br>• Need for SABA reliever ≤2 days per week†<br>• No limitation of activities<br>• No symptoms during night or on waking | One or two of:<br>• Daytime symptoms >2 days per week<br>• Need for SABA reliever >2 days per week†<br>• Any limitation of activities<br>• Any symptoms during night or on waking | Three or more of:<br>• Daytime symptoms >2 days per week<br>• Need for SABA reliever >2 days per week†<br>• Any limitation of activities<br>• Any symptoms during night or on waking |

SABA: short-acting beta$_2$-agonist

† SABA, not including doses 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 beta$_2$ agonists may, itself, increase the risk of asthma flare-ups:[8, 9]

Regular use of short-acting beta$_2$ 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.[10]

- Data from population and case-control studies has led to concerns that the frequent use of short-acting beta$_2$ agonists, including salbutamol, is associated with increased risk of asthma deaths.[4] 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 microg/day (10 puffs).
- Dispensing of 3 or more canisters of short-acting beta$_2$ agonist in a year (average 1.6 puffs per day) is associated with increased risk of flare-ups[11] Dispensing 12 or more canisters in a year (average 6.6 puffs per day) is associated with increased risk of asthma death.[12]

When high doses of short-acting beta$_2$ 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.

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### *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 beta$_2$ 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 microg or 200/6 microg
- pressurised metered-dose inhaler (*Symbicort Rapihaler*) 50/3 microg or 100/3 microg.

Neither the 400/12 microg dry-powder inhaler nor the 200/6 microg 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 beta$_2$ 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 beta$_2$ 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 beta$_2$ 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 beta$_2$ agonist combinations, leukotriene receptor antagonists, xanthines or any other asthma medicines) with rapid-onset beta$_2$ 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.

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

Inhaled beta$_2$-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 beta$_2$ 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 beta$_2$ agonists may actually increase the severity of exercise-induced bronchoconstriction.[24]

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

Intermittent short-acting beta$_2$ 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 microg 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 beta$_2$ 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*

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*Salbutamol in acute asthma*

## Route of administration
## Inhaler plus spacer, or nebuliser

Among patients with acute asthma who do not require mechanical ventilation, salbutamol delivered via a pressurised metered-dose inhaler with spacer is at least as effective as salbutamol delivered via nebuliser in preschool children (with viral-induced wheezing or acute asthma)[25] and adults,[2627] and is equivalent or superior in school-aged children.[28, 26, 29, 30]

The use of nebulisers increases the risk of transmitting respiratory infections to staff and other patients,[31] and increases the risk of adverse effects.

## Intravenous salbutamol

IV salbutamol is generally reserved for use in patients with severe acute asthma that does not respond to inhaled bronchodilators.

## Efficacy

Overall, intravenous short-acting beta$_2$ agonists do not appear to be superior to inhaled short-acting beta$_2$ agonist.[32]

## Adults

Benefits have not been demonstrated in adults.[32]

## Children

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.[32]

However, there is a lack of consensus on the appropriate dose of IV salbutamol for children.[33] Recommendations differ between guidelines in Australia[34] and elsewhere.[33] 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.

## Adverse effects

Compared with inhaled salbutamol, intravenous salbutamol is associated with increased risk of adverse effects including tremor and hypokalaemia.[32, 33] Concomitant use of the inhalation and IV routes may increase the risk of salbutamol toxicity.[35]

**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 microg salbutamol in 1 mL sterile isotonic solution (*Ventolin injection*).

## Salbutamol dosing regimens

There is very little evidence from clinical trials to guide dosing intervals for salbutamol treatment in acute asthma.

One placebo-controlled study conducted in the emergency department among adults with acute asthma ($FEV_1$ <60% predicted or normal) showed that, in those 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.[36] However, 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).[36]

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*Beta-2 receptor tolerance*

## Short-acting beta$_2$ agonists

In laboratory studies, regular use of short-acting beta$_2$ agonists leads to receptor tolerance (down-regulation) to their bronchoprotective and bronchodilator effects.[10]

In clinical trials, regular use of short-acting beta$_2$ agonists is associated with greater instability of lung function and a higher risk of asthma flare-ups.[37, 38]

In clinical practice, frequent use of short-acting beta$_2$-agonists may lead to worsening of asthma symptoms. This may be improved by

deliberately reducing short-acting beta$_2$ agonist use and, in some cases, using ipratropium bromide as an alternative reliever medicine medication to allow restoration of beta$_2$-receptor responsiveness.[39]

### Long-acting beta$_2$ agonists

In laboratory studies, regular use of long-acting beta$_2$ agonists results in reduced duration of protection against airway hyperresponsiveness, and prolonged recovery of airway function after short-acting beta$_2$ agonist, which is thought to be due to receptor tolerance (down-regulation) of beta$_2$ receptors in bronchial smooth muscle and mast cells (evidence from laboratory studies).[40] These findings have led to concerns about reduced effectiveness of beta$_2$ agonists when needed for preventing exercise-induced bronchoconstriction or reversing acute asthma due to trigger exposure.[40] Sensitivity to short-acting beta$_2$ agonists returns to normal within 72 hours of stopping long-acting beta$_2$ agonist treatment.[40]

However, the clinical effects of beta receptor tolerance in patients taking long-acting beta$_2$ agonists are unclear.[41] Clinical trials assessing regular use of long-acting beta$_2$ agonists in combination with inhaled corticosteroids have not reported clinically significant adverse effects attributable to beta receptor tolerance.[42] Two Emergency Department studies in patients with acute asthma did not observe increased risk of hospitalisation among those taking salmeterol.[43, 44]

The use of budesonide/formoterol as a reliever may result in lower total use of beta$_2$ agonist compared with the use of short-acting beta$_2$ agonist relievers, based on a study in patients taking regular maintenance budesonide/formoterol, which monitored inhaler actuations electonically.[20]

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# 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 beta$_2$ 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: http://www.asthmahandbook.org.au/table/show/79**

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*Montelukast*

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# 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: efficacy*

## Role in treatment asthma in children

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.[1] Overall, inhaled corticosteroids seem to be more effective in older children and those with more severe disease.[2]

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.[2]

Current evidence does not support planned seasonal use of inhaled corticosteroids in children not taking preventer at other times.[3]

*Children aged 1–5 years*

### Intermittent wheeze/asthma

In preschool children who only have wheezing episodes with viral respiratory infections, 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.[1, 4] Inhaled corticosteroid treatment does not reduce these children's risk of developing persistent wheeze by age 6 years.[5]

### Persistent wheeze/asthma

In preschool children who have episodes of wheezing from time to time, but also cough and wheezes at other times when they do not have a viral cold (e.g. when cries, plays or laughs), regular inhaled corticosteroids are moderately effective in controlling symptoms, though less effective than in older children.[5] When 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 spontaneous resolution of symptoms.[5] However, this can be clarified by stopping inhaled corticosteroid treatment, monitoring symptoms, and re-starting.

In infants and preschoolers with persistent wheezing or asthma of at least 6 months' duration, regular treatment with inhaled corticosteroids improves wheezing, asthma symptoms and lung function, and reduces flare-ups.[2, 6]

*Children aged 6 years and over*

Most clinical trials of regular inhaled corticosteroid treatment in children have been conducted among children with asthma symptoms every week or more often ('persistent asthma').[2]

Beclometasone dipropionate, budesonide, ciclesonide and fluticasone propionate have all been shown to be effective in children. There have been relatively fewer studies of ciclesonide in children,[2] but, overall, randomised clinical trials show that it is equally effective as budesonide or fluticasone propionate in improving asthma symptoms and reducing flare-ups.[7] In some studies, ciclesonide was associated with less adrenal suppression or height than comparator inhaled corticosteroids.[7]

In a study of school-aged children with more than 2 days per week with symptoms, night waking more than twice per month due to asthma symptoms, or needing regular preventer, regular low-dose daily inhaled corticosteroid treatment reduced the rate of flare-ups that require treatment with oral corticosteroids, compared with no regular preventer treatment and as-needed short-acting

beta$_2$agonist for wheezing episodes.[8]

In a study of children aged 4–11 years with asthma diagnosed within the previous 2 years and symptoms more than weekly in the previous 3 months, regular preventer was associated with a reduction in serious flare-ups, school absence due to asthma, an increase in symptom-free days, and improved lung function, compared with placebo.[9, 10]

The Thoracic Society of Australia and New Zealand's current position statement on the use of inhaled corticosteroids in children[2] recommends regular treatment with inhaled corticosteroid:

- as a first-choice preventer for children with asthma symptoms at least daily or night-time symptoms at least twice per week between flare-ups
- as an alternative to cromones (nedocromil or sodium cromoglycate) or montelukast in children with any daytime or night-time symptoms between flare-ups, or those with flare-ups every 6 weeks or more.

### *Doses*

In the majority of children, asthma control can be achieved with any of the following initial doses:[2]

- budesonide up to 400 microg/day
- beclometasone (*Qvar*) up to 200 microg/day
- ciclesonide up to 160 microg/day
- fluticasone propionate up to 200 microg/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.[2]

Dose–response studies of inhaled corticosteroids show that the maximal efficacy is generally achieved at a dose equivalent to approximately 200 microg/day fluticasone propionate,[2] while the risk of adrenal suppression increases exponentially at doses above 500 microg/day.[2] Therefore (based on theoretical equivalents between different agents), upper limits of daily doses for children are:

- budesonide 800 microg/day
- beclometasone dipropionate [*Qvar*] 400 microg/day
- ciclesonide 320 microg/day
- fluticasone propionate 500 microg/day.

Higher doses are unlikely to be more effective, and are likely to cause systemic effects.[2]

Most studies of inhaled corticosteroids in children have used twice-daily dosing.[2] Fluticasone propionate is only approved for twice-daily dosing, but the other inhaled corticosteroids are approved for once daily dosing. Ciclesonide is effective when given once daily.[2]

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

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

| Inhaled corticosteroid | Daily dose (microg) | |
|---|---|---|
| | **Low** | **High** |
| *Beclometasone dipropionate* † | 100–200 | >200 (maximum 400) |
| *Budesonide* | 200–400 | >400 (maximum 800) |
| *Ciclesonide* ‡ | 80–160 | >160 (maximum 320) |
| *Fluticasone propionate* | 100–200 | >200 (maximum 500) |

† 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*

van Asperen PP, Mellis CM, Sly PD, Robertson C. *The role of corticosteroids in the management of childhood asthma*. The Thoracic Society of Australia and New Zealand, 2010. Available from: http://www.thoracic.org.au/clinical-documents/area?command=record&id=14

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### *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.[1, 4] Inhaled corticosteroid treatment does not reduce these children's risk of developing persistent wheeze by age 6 years.[5]

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.[2, 6]

In preschool children with multiple-trigger wheeze, regular inhaled corticosteroids are moderately effective in controlling symptoms, but less effective than in older children.[5] 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.[5]

### *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.[2] 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)[2] but, overall, randomised clinical trials show that it is equally effective as budesonide or fluticasone propionate in improving asthma symptoms and reducing flare-ups.[7]

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 $beta_2$ agonist for wheezing episodes.[8]

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.[2]

### *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 $beta_2$ agonist)
- ciclesonide (low to high doses available)
- fluticasone furoate (medium to high doses available, including in combination with a long-acting $beta_2$ agonist)
- fluticasone propionate (low to high doses available, including in combination with a long-acting $beta_2$ agonist)

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

| Inhaled corticosteroid | Daily dose (microg) | | |
|---|---|---|---|
| | Low | Medium | High |
| *Beclometasone dipropionate †* | 100–200 | 250–400 | >400 |
| *Budesonide* | 200–400 | 500–800 | >800 |
| *Ciclesonide* | 80–160 | 240–320 | >320 |

| Inhaled corticosteroid | Daily dose (microg) | | |
|---|---|---|---|
| | Low | Medium | High |
| *Fluticasone furoate** | — | 100 | 200 |
| *Fluticasone propionate* | 100–200 | 250–500 | >500 |

† 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*

Respiratory Expert Group, Therapeutic Guidelines Limited. *Therapeutic Guidelines: Respiratory, Version 4*. Therapeutic Guidelines Limited, Melbourne, 2009.

GlaxoSmithKline Australia Pty Ltd. Product Information: *Breo (fluticasone furoate; vilanterol) Ellipta*. Therapeutic Goods Administration, Canberra, 2014. Available from: https://www.ebs.tga.gov.au/

GlaxoSmithKline Australia Pty Ltd. Product Information: *Arnuity (fluticasone furoate) Ellipta*. Therapeutic Goods Administration, Canberra, 2016. Available from: https://www.ebs.tga.gov.au/

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## Clinical benefits

Inhaled corticosteroids are the most effective preventer medicines for adults.[11]

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.[12, 13, 14, 15, 16, 17, 18, 19, 20, 21]

## 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 microg/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).[15, 17, 18]
- 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 microg/day) improved lung function,[22] reduced airway hyperresponsiveness and inflammation,[22, 23] and reduced the risk of mild flare-ups.[22, 23]

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).[19] In that study, breaks in the use of inhaled corticosteroid of up to 3 months were associated with increased risk of death.[20]
- In adults and adolescents with mild asthma who were not taking inhaled corticosteroids, starting low-dose inhaled corticosteroid (budesonide 200 microg/day) reduced the risk of asthma flare-ups severe enough to require oral corticosteroids, and improved symptom control (evidence from a large clinical trial).[16]
- 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 microg/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). [15, 17, 18]

**Note:** PBS status as at March 2019: 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:[2]

- budesonide 400 microg/day
- beclometasone (*Qvar*) 200 microg/day
- ciclesonide 160 microg/day
- fluticasone propionate 200 microg/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.[2]

Dose–response studies of inhaled corticosteroids show that the maximal efficacy is generally achieved at a dose equivalent to approximately 200 microg/day fluticasone propionate,[2] while the risk of adrenal suppression increases exponentially at doses above 500 microg/day.[2] Therefore (based on theoretical equivalents between different agents), upper limits of daily doses for children are:

- budesonide 800 microg/day
- beclometasone dipropionate [*Qvar*] 400 microg/day
- ciclesonide 320 microg/day
- fluticasone propionate 500 microg/day.

Higher doses are unlikely to be more effective, and are likely to cause systemic effects.[2]

Most studies of inhaled corticosteroids in children have used twice-daily dosing.[2] Ciclesonide is effective when given once daily.[2] 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.[2]

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

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

| Inhaled corticosteroid | Daily dose (microg) | |
|---|---|---|
| | **Low** | **High** |
| *Beclometasone dipropionate †* | 100–200 | >200 (maximum 400) |
| *Budesonide* | 200–400 | >400 (maximum 800) |
| *Ciclesonide ‡* | 80–160 | >160 (maximum 320) |
| *Fluticasone propionate* | 100–200 | >200 (maximum 500) |

† 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*

van Asperen PP, Mellis CM, Sly PD, Robertson C. *The role of corticosteroids in the management of childhood asthma.* The Thoracic Society of Australia and New Zealand, 2010. Available from: http://www.thoracic.org.au/clinical-documents/area?command=record&id=14

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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 microg budesonide per day,[24, 25] 200 microg HFA beclometasone, 160 microg ciclesonide or 200 microg fluticasone propionate).

On average, higher doses provide relatively little extra benefit, but are associated with a higher risk of adverse effects.[26] However, a small proportion of individuals may need a higher dose to achieve asthma control.[26, 24, 25]

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 microg/day for fluticasone propionate, 400–800 microg/day for budesonide, or 200–400 microg/day beclometasone.[27]
- A starting dose higher than 800 microg/day budesonide, 400 microg/day fluticasone propionate, or 400 microg beclometasone does not provide enough clinical benefit over lower doses to warrant routinely starting with high doses.[27]
- Starting with a moderate dose of inhaled corticosteroid is as effective as commencing with a high dose and down-titrating.[27] 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,[27] but this may not equate to a clinical benefit.

Meta-analyses[28, 29] 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.

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

| Inhaled corticosteroid | Daily dose (microg) | | |
|---|---|---|---|
| | Low | Medium | High |
| *Beclometasone dipropionate †* | 100–200 | 250–400 | >400 |
| *Budesonide* | 200–400 | 500–800 | >800 |
| *Ciclesonide* | 80–160 | 240–320 | >320 |
| *Fluticasone furoate** | — | 100 | 200 |
| *Fluticasone propionate* | 100–200 | 250–500 | >500 |

† 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*

Respiratory Expert Group, Therapeutic Guidelines Limited. *Therapeutic Guidelines: Respiratory, Version 4*. Therapeutic Guidelines Limited, Melbourne, 2009.

GlaxoSmithKline Australia Pty Ltd. Product Information: *Breo (fluticasone furoate; vilanterol) Ellipta*. Therapeutic Goods Administration, Canberra, 2014. Available from: https://www.ebs.tga.gov.au/

GlaxoSmithKline Australia Pty Ltd. Product Information: *Arnuity (fluticasone furoate) Ellipta*. Therapeutic Goods Administration, Canberra, 2016. Available from: https://www.ebs.tga.gov.au/

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## *Inhaled corticosteroids for children: adverse effects*

### *Local adverse effects*

Hoarseness and pharyngeal candidiasis are not commonly reported among preschool children or school-aged children talking inhaled corticosteroids. [5, 2, 30]

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.[31]

There is limited evidence that inhaled asthma medication can affect dental health.[2, 32] Mouth rinsing might reduce this risk.

### *Systemic adverse effects*

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 the use of a spacer may increase efficacy so that a lower dose is required.

### Growth

Short-term suppression of linear growth has been demonstrated in children taking inhaled corticosteroids.[33,34] The effect seems to be maximal during the first year of therapy and only one study has reported an effect in subsequent years of treatment.[34] A Cochrane systematic review concluded that regular use of inhaled corticosteroid at low or medium daily doses is associated with a mean reduction of 0.48 cm per year in linear growth velocity and 0.61 cm less gain in height during 1 year of treatment in children with mild to moderate persistent asthma.[34]

One study of patients who participated in a clinical trial of inhaled corticosteroids as children, reported a reduction in adult height of approximately 1 cm,[33, 35, 36, 37] whereas several studies have reported that children taking inhaled corticosteroids attained normal adult height.[18, 38, 39]

The effect is dose-dependent[36,37] and may be more likely in children who begin inhaled corticosteroid treatment before age 10.[35]

Other factors affect growth in children with asthma. Uncontrolled asthma itself reduces growth and final adult height.[40] One study found that inhaled corticosteroid equivalent to budesonide 400 microg/day affected growth less than low socioeconomic status.[39]

### Bone density

Inhaled corticosteroids have not been associated with effects on bone density or fractures in children. [2] However, data from a recent study in Australia suggested asthma itself is associated with increased incidence of fractures in children, independent of medication.[41]

Given that the total dose of corticosteroids (both inhaled corticosteroids and oral corticosteroids) influences bone health, the aim of asthma management is to maintain symptom control using the lowest inhaled corticosteroid dose required, and to avoid repeated courses of oral corticosteroids.

### Adrenal suppression

Biochemical testing in a research setting suggests 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.[42] The risk is higher among children receiving concomitant intranasal steroids and those with lower body mass index,[42] and is influenced by genetics.[43]

Clinical adrenal insufficiency in children taking inhaled corticosteroids is rare but has been reported, [44, 45, 46] including cases in Australia.[46] Most cases have involved children given more than 500 microg per day fluticasone propionate.[44]

Adrenal suppression is associated with hypoglycaemia, hypotension, weakness, failure to grow, and is potentially fatal. Hypothalamic–pituitary–adrenal axis suppression may not be detected until adrenal crisis is precipitated by physical stress.[47]

Written information (e.g. a steroid alert card) can be prepared for children receiving long-term high-dose inhaled corticosteroids. Parents/carers can be instructed to present the card if the child ever needs to go to the emergency department (for any reason) or be admitted to hospital. A steroid alert card should state that child has asthma and the inhaled corticosteroid dose. A medical alert bracelet could also be considered.

There are no nationally accepted protocols for routine assessment of adrenal function in primary care 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.

Regular monitoring of height might help detect adrenal suppression, based on the findings of a study in which a reduction in linear growth velocity occurred before adrenal suppression.[48]

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

| Inhaled corticosteroid | Daily dose (microg) | |
|---|---|---|
| | Low | High |
| *Beclometasone dipropionate* † | 100–200 | >200 (maximum 400) |
| *Budesonide* | 200–400 | >400 (maximum 800) |
| *Ciclesonide* ‡ | 80–160 | >160 (maximum 320) |
| *Fluticasone propionate* | 100–200 | >200 (maximum 500) |

† 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*

van Asperen PP, Mellis CM, Sly PD, Robertson C. *The role of corticosteroids in the management of childhood asthma*. The Thoracic Society of Australia and New Zealand, 2010. Available from: http://www.thoracic.org.au/clinical-documents/area?command=record&id=14

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▶ Go to: The Thoracic Society of Australia and New Zealand's *Position Statement: The role of corticosteroids in the management of childhood asthma*

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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:[49]

- The rate of of dysphonia among patients taking inhaled corticosteroids has been estimated at 5–20%.[50] However, higher rates of up to 58% have been reported in some studies.[51] 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.[50]

When taking inhaled corticosteroids via pressurised metered-dose inhalers, the use of a spacer reduces the risk of dysphonia and candidiasis.[52] Spacers improve delivery of the medicine to the airways.

Quick mouth rinsing immediately after inhaling effectively removes a high proportion of remaining medicine.[31] This may reduce the risk of oropharyngeal candidiasis ('thrush').

The incidence of dysphonia and candidiasis is significantly lower with ciclesonide than with equivalent doses of fluticasone propionate.[53] 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.[54]

▶ Go to: National Asthma Council Australia's *Inhaler technique in adults with asthma or COPD* information paper

### Systemic adverse effects

Cross-sectional population studies have reported lower bone mineral density with long-term use of high doses of inhaled corticosteroid,[55] 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.[56]

Cross-sectional studies show a dose–response relationship between inhaled corticosteroid use for asthma or COPD, and risk of cataracts in adults.[57]

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 microg/day or higher).[58]

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.

▶ Go to: Australian and New Zealand Bone and Mineral Society's *Vitamin D and health in adults in Australia and New Zealand: a position statement*
Go to: Osteoporosis Australia's *Building healthy bones throughout life: an evidence-informed strategy to prevent osteoporosis in Australia*

### Patient concerns about adverse effects

The prevalence of side effects that patients consider troubling increases with increasing dose of inhaled corticosteroids.[59] Mid and high doses are consistently associated with a higher intensity and a higher prevalence of reported adverse effects, after controlling for other factors.[59]

A high proportion of people with asthma may have misunderstandings and fears about using inhaled corticosteroids,[60, 61] such as fears about weight gain, unwanted muscle development, bone fractures, susceptibility to infections and reduction of efficacy of the medicine over time.[60] Most people do not discuss their concerns about inhaled corticosteroid treatment with health professionals.[60] Safety concerns are a major reason for poor adherence, particularly general concerns about corticosteroids rather than concerns about specific adverse effects.[62]

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### *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,[63] and are potentially distributed more widely in the large, intermediate, and small airways.[63] Although there are theoretical advantages with fine-particle formulations, including in severe asthma, the clinical implications have not been established.[64]

Randomised controlled trials comparing ciclesonide with fluticasone propionate in adults and adolescents have observed lower rates of patient-reported side-effects,[65] and confirmed dysphonia and oral candidiasis,[53] among patients using ciclesonide than among those using fluticasone propionate.

A small randomised controlled trial reported that ciclesonide treatment reduced sputum eosinophil counts in patients with refractory asthma who has previously shown persistent airway eosinophilia despite high-dose inhaled corticosteroids.[66] However, this study did not provide any comparison with a higher dose of the patient's existing inhaled corticosteroid.

Evidence from clinical trials of ciclesonide is limited. There have been no high quality double-blind studies to date, and observational studies have not been properly designed to avoid confounding factors such as prescriber bias.[64]

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### *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.[67, 68, 69, 70] Most of the available evidence is from patients treated with fluticasone propionate.[70, 71, 72, 73, 74, 75] Increased pneumonia rates have also been observed in studies of patients with COPD using fluticasone furoate/vilanterol.[76] The higher dose of fluticasone furoate/vilanterol (*Breo Ellipta* 200/25 microg) is not indicated for patients with COPD.

Increased risk of pneumonia with inhaled corticosteroids has not been established in patients with asthma.[76, 77] However, the risk of pneumonia in patients with asthma–COPD overlap is unknown, so caution is advised, particularly if high doses are being considered.

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### *Inhaled corticosteroids for exercise-induced bronchoconstriction*

Inhaled corticosteroids taken regularly long term (4 weeks or more[78]) are effective in reducing the frequency and severity of exercise-induced bronchoconstriction in 30–60% of people with asthma.[79] The degree of protection experienced by individuals ranges from complete to minimal.[79]

Patients may need to take inhaled corticosteroid for 12 weeks to experience maximal therapeutic effect.[79] If exercise-induced symptoms have resolved, the person may no longer need to take a $beta_2$ agonist before exercise.[79] However, some patients taking regular inhaled corticosteroids may still need to take short-acting $beta_2$ agonists before exercise.[79]

Few comparative studies have compared the effectiveness of inhaled corticosteroid with that of other classes of medicines.[78]

*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.[80]

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.[80] 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.[80]

### Inhaled corticosteroid treatment in post-acute care - short term effects

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 short term 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.[81]

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.[81]

These clinical trials were designed to assess short term 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.[81] Regular inhaled corticosteroid treatment is highly effective for preventing asthma flare-ups, including in patients with a recent asthma hospitalisation. A large case-control study showed that, after hospitalisation for asthma, regular ICS were associated with a 39% reduction in the risk of re-hospitalisation within the following 12 months.[82]

### Rationale for prescribing inhaled corticosteroids at discharge from acute care

Inhaled corticosteroid treatment reduces the frequency and severity of asthma flare-ups, reduces the risk of asthma hospitalisation and rehospitalisation, and reduces the risk of death due to asthma. [19, 83]

Regular inhaled corticosteroid treatment is therefore indicated for all adults and older adolescents who have experienced a flare-up within the last 12 months, as well as for those with asthma that is not well controlled (asthma symptoms twice or more during the past month, or waking due to asthma symptoms once or more during the past month).

At the time of discharge from the emergency department or hospital, there is an opportunity to start inhaled corticosteroid treatment and to ensure that the patient's usual GP will review the treatment regiment at the follow-up visit.

▶ See: *Prescribing inhaled corticosteroid-based preventers for adults*

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*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$_2$ agonist combination.

**Table. Step-up options for children when good asthma control is not achieved with low-dose ICS**

| Option | TGA-registered indications for add-on therapy | PBS considerations |
|---|---|---|
| *High-dose ICS* | N/A | Subsidised |
| *ICS plus montelukast* | 2 years and over | 2–5 years: not subsidised*<br>6–14 years: not subsidised unless for |

| Option | TGA-registered indications for add-on therapy | PBS considerations |
|---|---|---|
| | | exercise-induced bronchoconstriction despite ICS treatment† <br> 15 years and over: not subsidised‡ |
| *ICS/long-acting beta$_2$ agonist combination* | 4 years and over for fluticasone propionate/ salmeterol xinafoate <br> 12 years and over for budesonide/formoterol fumarate dihydrate | Subsidised |

- 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.

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In the majority of children with persistent asthma that requires preventive treatment, control can be achieved with one of these options.[2]

Few studies have been conducted in preschool-aged children. The preferred step-up option for children aged 6–12 years is controversial and guidelines differ in their recommendations.[84]

### Increasing inhaled corticosteroid dose versus adding a long-acting beta$_2$ agonist

In school-aged children with persistent asthma taking regular inhaled corticosteroid, the addition of a long-acting beta$_2$ agonist does not reduce the rate of asthma flare-ups requiring systemic steroids compared with the same or higher doses of inhaled corticosteroid.[85, 86] However, the long-acting beta$_2$ agonist–inhaled corticosteroid was superior for improving lung function.[85] Growth is reduced in children treated with higher-dose inhaled corticosteroid, compared with those taking same dose plus a long-acting beta$_2$ agonist.[85]

Adolescents may benefit more from combination inhaled corticosteroid/long-acting beta$_2$ agonist treatment than children under 12 years. 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.[87]

*Adding montelukast versus adding a long-acting beta-2 agonist or increasing inhaled corticosteroid dose*

### Children aged 1–5 years

In one study in children aged 5 years or less with persistent asthma/wheeze requiring preventer treatment, raised blood eosinophil levels and atopy predicted better short-term response to high-dose inhaled corticosteroid than to montelukast.[88] However, routine eosinophil counts are currently not recommended to guide treatment in children.

In children aged 1–5 years with asthma/wheeze that is not adequately controlled by low-dose inhaled corticosteroid alone, adding montelukast is preferable to increasing the dose of inhaled corticosteroids when the safety profiles of these options are compared.[89] Long-acting beta$_2$ agonists are not recommended for this age group.

- Montelukast use has been associated with behavioural and/or neuropsychiatric adverse effects.

▶ Go to: TGA alert

Note: Montelukast is TGA-approved for children aged 2 years and over.

### Children aged 6 years and over

Among children 6 years and over with asthma that is not controlled by low-dose inhaled corticosteroids, the optimal regimen varies

between individuals.[90] In one study of children selected for high adherence with maintenance treatment, short-term responses varied between individuals: in some children the best response was achieved by adding a long-acting beta$_2$ agonist, in others by adding montelukast, and in others by increasing the dose of inhaled corticosteroid.[90]

Note: The use of inhaled corticosteroids and long-acting beta$_2$ agonists in separate inhalers is not recommended for either children or adults because of the potential for increased risk due to selective non-adherence to the inhaled corticosteroid.[91]

Overall, the addition of montelukast to an inhaled corticosteroid does not reduce the need for rescue oral corticosteroids or hospital admission, compared with the same or an increased dose of inhaled corticosteroids, in children aged 6 years and over or adolescents with mild-to-moderate asthma.[92]

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.[93] 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.[93]

A treatment trial of montelukast for 4–6 weeks is the best option when effects on exercise-induced symptoms and safety are also considered.[89]

- Montelukast use has been associated with behavioural and/or neuropsychiatric adverse effects.

▶ Go to: TGA alert

See: *Investigation and management of exercise-induced bronchoconstriction*

### Genetic influence on effect of long-acting beta$_2$ agonists

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.[94] However, routine genetic testing to tailor asthma therapy is not yet available in clinical practice.

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### *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 beta$_2$ agonist combination treatment.

There is some evidence that quadrupling the maintenance dose of inhaled corticosteroids,[95] or treating with a high dose of inhaled corticosteroids,[96, 97, 98] reduces the severity of asthma flare-ups. For patients taking inhaled corticosteroid/long-acting beta$_2$ 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.[99]
- 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.[100] 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,[95] 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.[95] 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.[95]

### *Increasing the inhaled corticosteroid dose to control flare-ups in children*

In children taking regular inhaled corticosteroid-containing preventers, there is conflicting evidence for whether, and by how much, the dose should be increased when symptoms worsen or at the onset of an acute flare-up.

Overall, current evidence from highly controlled randomised controlled trials does not support increasing the dose of inhaled corticosteroid as part of a self-initiated action plan to manage flare-ups in children younger than 12 years.[101]

There is some evidence that high doses of inhaled steroids used pre-emptively might be effective in preventing severe acute asthma in children aged under 5 years, based on studies in children not taking regular inhaled corticosteroids.[102] However, very high pre-emptive doses affect children's growth[103] and are not recommended.

Recent randomised controlled trials reported a lack of effect with a range of dose increases:

- A five-fold increase in the inhaled corticosteroid dose at early signs of worsening asthma did not reduce the rate of severe acute asthma in children aged 5–11 years with well-controlled asthma while taking maintenance inhaled corticosteroid treatment (with high adherence).[104] This strategy was associated with a small reduction in linear growth.[104]
- Dose increases of four or eight times usual inhaled corticosteroid maintenance dose at the onset of an acute flare-up in children aged 2–17 years did not reduce requirement for oral corticosteroids, compared with doubling the dose.[105]

A Cochrane systematic review[101] in children and adults reported that increasing the inhaled corticosteroid dose did not prevent severe flare-ups, regardless of how soon the increase was initiated after the onset of symptoms or the magnitude of the dose increase (doubling versus quadrupling). The results did not differ between children under 15 and adults or older adolescents.[101] However, there were too few studies in children to make firm conclusions.

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# 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: http://www.asthmahandbook.org.au/table/show/79**

## More information

### *Inhaled corticosteroid/long-acting beta-2 agonist combinations for children aged 4–11 years*

The combination of salmeterol plus fluticasone propionate in a single inhaler is TGA-registered for use in children 4 years and older.

#### *Efficacy*

A very large (n=6208) randomised controlled trial in children aged 4–11 years reported that, unlike in adults, the combination of inhaled corticosteroid and long-acting beta$_2$ agonist was not associated with a significant reduction in severe flare-ups, compared with inhaled corticosteroid alone.[1] Combination treatment was not associated with an increase in in symptom-free days or a reduction in reliever use, compared with inhaled corticosteroid alone.[1]

#### *Safety*

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.[2, [REPLACE THIS REF]] However, routine genetic testing to tailor asthma therapy is not yet available in clinical practice.

Earlier systematic reviews and meta-analyses 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.[4,5, 6] A meta-analysis commissioned 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 beta$_2$ agonist), and that this risk was greatest in children aged 4–11 years.[6] However, the increased risk was only seen in studies where inhaled corticosteroid was not provided, or where inhaled corticosteroid and long-acting beta$_2$ agonist were not combined in a single inhaler (i.e. where there was the possibility of selective non-adherence to the inhaled corticosteroid).

The PBAC Post-market review of medicines used to treat asthma in children[3] concluded that there was insufficient evidence to ascertain whether tolerance to long-acting beta$_2$ agonist could explain why it is less effective than montelukast and inhaled corticosteroids in managing exercise-induced asthma symptoms.[3]

A very large randomised controlled trial of children aged 4–11 years, stratified by asthma symptom control and pre-study treatment, found no increased risk of serious adverse outcomes with combination fluticasone propionate and salmeterol in a single inhaler, compared with fluticasone propionate alone.[1] Subsequent to the publication of this and similar studies in adults,[CHECK THIS REF] regulators in the USA and Australia removed previous 'black box' warnings from combination inhaled corticosteroid–long-acting beta$_2$ agonist products for asthma.[CHECK THIS REF]

PBS status as at March 2019: All formulations that contain a combination of inhaled corticosteroid plus long-acting beta$_2$ agonist are listed as 'Authority required - streamlined'. Patient using these combinations for asthma must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids.

*Last reviewed version 2.0*

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

- To avoid the possibility of patients taking a long-acting beta$_2$ agonist without an inhaled corticosteroid, long-acting beta$_2$ agonists should (whenever possible) be prescribed as inhaled corticosteroid/long-acting beta$_2$ 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 beta$_2$ agonist:[9]

- 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.[9]

Each of the following inhaled corticosteroid/long-acting beta$_2$ 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 beta$_2$ 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.[10] Most of the evidence for inhaled corticosteroid/long-acting beta$_2$ 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.[11] In adults and adolescents already taking inhaled corticosteroids, once-daily fluticasone furoate/vilanterol 100/25 microg reduced the risk of severe flare-ups (requiring oral corticosteroids or hospitalisation) and improved lung function, compared with fluticasone furoate alone.[12] Efficacy data for the comparison of fluticasone furoate/vilanterol with other inhaled corticosteroid/long-acting beta$_2$ agonist combinations is not available.
- In adults and adolescents with persistent asthma and $FEV_1$ 50–80% at baseline, fluticasone propionate/formoterol achieved improvement in $FEV_1$ comparable to that achieved with budesonide/formoterol in a 12-week randomised double-blind clinical trial.[13] 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,[14] and was as effective as fluticasone propionate/salmeterol in adults.[15]

Long-acting beta$_2$ agonists should not be used without inhaled corticosteroids in the management of asthma.[16, 17, 18, 19] Long-acting beta$_2$ agonists are well tolerated when given in combination with inhaled corticosteroids.[10, 20]

### 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 beta$_2$ agonist reliever), in addition to its use as regular maintenance treatment.

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*Inhaled corticosteroid/long-acting beta-2 agonist combinations for exercise-induced bronchoconstriction*

- To avoid the possibility of patients taking a long-acting beta$_2$ agonist without an inhaled corticosteroid, long-acting beta$_2$ agonists should (whenever possible) be prescribed as inhaled corticosteroid/long-acting beta$_2$ 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 beta$_2$ agonists administered by inhalation before exercise are effective in protecting against exercise-induced bronchoconstriction:[21]

- for formoterol, onset of bronchodilation and bronchoprotective action is 1-3 minutes after administration[22]
- for salmeterol, onset of bronchodilation and bronchoprotective action is 10 - 30 minutes after administration[23]

The duration of effect of both formoterol and salmeterol is up to 12 hours for patients who have not taken a short-acting beta$_2$ agonist or long-acting beta$_2$ agonist within the previous 72 hours. However, the duration of bronchoprotection is reduced for subsequent doses due to receptor tolerance.[21]

### *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 beta$_2$ agonist reliever), in addition to its use as regular long-term preventer treatment.[24, 25, 26, 27, 28, 29] The following formulations can be used in maintenance-and-reliever regimens:

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

Neither the 400/12 microg dry-powder inhaler nor the 200/6 microg 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.[30]

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:[26]

- higher-dose budesonide
- same dose budesonide/formoterol
- higher-dose inhaled corticosteroid/long-acting beta$_2$ 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 beta$_2$ agonist reliever as needed):[26, 31, 32]

- 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 beta$_2$ agonist.[33]

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 beta$_2$ agonist combinations, leukotriene receptor antagonists, xanthines or any other asthma medicines) with rapid-onset beta$_2$ agonist reliever (selected according to clinician's choice).[34] 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.

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### *Managing flare-ups in adults: adjusting budesonide/formoterol maintenance-and-reliever treatment*

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

- for budesonide/formoterol 100/6 microg or 200/6 microg via dry-powder inhaler, up to a maximum of 12 actuations per day (total of maintenance and reliever inhalations) [25]
- for budesonide/formoterol 50/3 microg or 100/3 microg via pressurised metered-dose inhaler, up to a maximum of 24 actuations per day (total of maintenance and reliever inhalations).[35]

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*

*Last reviewed version 2.0*

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# 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: http://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.[1] 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.[1]

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.[2]

Montelukast may improve lung function, reduce short-acting beta2 bronchodilator use, reduce symptoms, and improve quality of life in patients with aspirin-exacerbated respiratory disease.[3]

Montelukast is sometimes prescribed as add-on treatment for adults with severe asthma. Current evidence does not support its long-term use unless the patient shows a clear improvement in symptoms during a treatment trial.[4]

▶ Go to: *Investigation and management of exercise-induced bronchoconstriction*

**Note:** PBS status as at March 2019: 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.

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### *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.[5] 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.[5]

▶ Go to: *TGA alert*

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### *Montelukast for children: efficacy*

- Montelukast use has been associated with behavioural and/or neuropsychiatric adverse effects, including suicidality.

▶ Go to: TGA alert

#### *Overview*

Montelukast is a leukotriene receptor antagonist preventer. It is registered by the TGA for the treatment of asthma in children aged 2

years and older, and for the symptomatic treatment of allergic rhinitis.[6]

Montelukast can be used as an alternative to inhaled corticosteroids or as an add-on treatment in a child already taking regular inhaled corticosteroids.

However, it is not effective for all children. Overall, only approximately 20–30% of children will respond to montelukast treatment. The effect is thought to depend mainly on the child's genotype.[7, 8, 9] Clinically, it is not possible to predict accurately which children will benefit most from montelukast treatment.

### *Montelukast as first-line preventer in children aged 2–5 years*

## Viral-induced wheezing

Overall, regular maintenance montelukast treatment does not reduce the risk of wheezing episodes requiring oral corticosteroid treatment among preschool children who only have wheezing episodes when they have viral upper respiratory tract infections.[10]

However, montelukast may be effective for some children. Some randomised controlled trials have reported a reduction the risk of flare-ups in preschool children with intermittent asthma/wheeze,[11, 12] while others have not.[13]

## Persistent asthma or wheezing

A systematic review comparing montelukast with inhaled corticosteroids in preschoolers with asthma or recurrent wheezing requiring daily preventer treatment[14] reported that inhaled corticosteroids appeared to achieve better symptom control and reduce flare-ups (including severe flare-ups requiring treatment with systemic corticosteroids). However, results were inconsistent and meta-analysis was not possible due to heterogeneity of outcomes measured in available clinical trials.[14]

Some preschool children with persistent asthma/wheeze respond to montelukast. A crossover study in preschool children with persistent asthma/wheeze reported that some children showed their best response to montelukast, while most responded better to regular inhaled corticosteroids.[15] Predictors of a better response to inhaled corticosteroids than montelukast were aeroallergen hypersensitivity and blood eosinophilia (eosinophil counts ≥ 300/μL).[15] However, routine blood eosinophil count is not feasible or recommended for this purpose.

### *Montelukast as first-line preventer children aged 6 years and over*

In school-aged children with persistent asthma, inhaled corticosteroids are more effective overall than montelukast in improving lung function and controlling asthma symptoms.[16, 18]

However, symptoms will respond to a treatment trial of montelukast in approximately one-quarter to one-third of children,[16, 19,20] and some may benefit more than from an inhaled corticosteroid.[16] More severe asthma and markers of allergic inflammation may predict a better response to inhaled corticosteroids.[16]

### *Montelukast as add-on treatment*

A systematic review of studies in children over 6 years and adolescents with mild-to-moderate persistent asthma found that the addition of montelukast to inhaled corticosteroids did reduce flare-ups requiring oral corticosteroids or hospital admissions for asthma, compared with the same or an increased dose.[18]

In a study comparing step-up treatments in children with asthma symptoms uncontrolled by low-dose inhaled corticosteroids, the addition of a long-acting beta$_2$ agonist was effective in more children than either montelukast or increasing the dose of inhaled corticosteroid for controlling asthma symptoms and preventing flare-ups requiring systemic corticosteroids.[21] However, some studies in school-aged children with persistent asthma already taking regular inhaled corticosteroids have reported that add-on montelukast reduced the risk of flare-ups[21, 22] and exercise-induced asthma symptoms.[22] Not all children will respond.

In a small study in children with persistent asthma already taking regular inhaled corticosteroids who were homozygous for the Arg16 genotype, montelukast was more effective as an add-on therapy than long-acting beta$_2$ agonist in reducing symptoms, reliever use and days absent from school due to asthma, depending on the child's beta receptor genotype.[9] However, children were given inhaled corticosteroid and long-acting beta$_2$ agonists in separate inhalers, which is which is known to be associated with increased risks.

However, genotyping it is not currently feasible in clinical practice. In practice, a treatment trial of 4–6 weeks can determine which preventer is suitable for controlling a child's asthma symptoms,[16] but longer treatment may be required to evaluate effect on flare-ups, because flare-ups may be independent of symptom control.

### *Exercise-induced symptoms*

In school-aged children who experience exercise-induced symptoms despite taking regular inhaled corticosteroids, the addition of montelukast is effective in controlling symptoms, but not all children experience a response.[23]

See: *Investigation and management of exercise-induced bronchoconstriction*

### *Short-term use in the management of flare-ups*

Some, but not all studies suggest that a short course of montelukast, introduced at the first signs of an upper respiratory tract infection,

may be effective in controlling flare-ups. An Australian study reported that this strategy could achieve a small reduction in symptoms, school absence and medical consultations in preschool and school-aged children with episodic wheeze.[24]

However, the evidence is inconsistent, with some studies showing no benefit.[13,25, 26, 27, 28] The findings of one study suggested that whether or not intermittent montelukast is effective in wheezing children aged 5 years and under depends on genotype.[8]

Montelukast is not TGA-approved or PBS-subsidised for intermittent use.

**Note:** PBS status as at March 2019: Montelukast is not subsidised by the PBS for adolescents 15 years and over.

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### *Montelukast for children: behavioural and/or neuropsychiatric adverse effects*

Montelukast is generally very well tolerated. Behavioural and psychiatric adverse effects were rare in clinical trials.[25, 29] However, post-marketing surveillance reports have identified behavioural and/or neuropsychiatric adverse effects associated with montelukast use in some children.[27]

Behavioural treatment-associated effects are difficult to assess in young children. No factors have been identified to predict which children are at risk.

Reported adverse events include nightmares, sleep disturbance, anxiety, irritability, aggression and depression.[27, 30, 8, 13]

Suicidal ideation has been reported in adolescents and adults taking montelukast.[13] A 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.[31]

Reported adverse effects are usually mild.[8] The majority occur within 7–14 days of starting montelukast,[27, 8] but some may appear after several months.[13]

Behavioural and/or neuropsychiatric adverse effects typically disappear within 4 days of stopping montelukast treatment.[8] There is no evidence of long term effects.

The TGA recommends that clinicians treating children with montelukast should educate caregivers about these potential adverse effects and should consider providing them with the CMI. Advise them to seek medical advice if they have any concerns.

▶ Go to: TGA's 2018 safety review of montelukast

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### *Montelukast for exercise-induced bronchoconstriction*

Montelukast is less effective against exercise-induced bronchoconstriction than short-acting beta$_2$ agonists, but regular use is not associated with receptor tolerance.[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.[2] Some experience strong protection against exercise-induced bronchoconstriction while others experience only partial protection or no effect.[2] Very few patients experience complete protection against exercise-induced bronchoconstriction.[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$_2$ agonists in protecting against exercise-induced bronchoconstriction,[32, 33] and is associated with a greater bronchodilator response to short-acting beta$_2$ agonist after exercise.[32]

The onset of protection occurs within 2 hours of dosing. The duration of protective effect is 12–24 hours. Recommended doses are as follows:[33]

- 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 March 2019: 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.

- Montelukast use has been associated with behavioural and/or neuropsychiatric adverse effects, including suicidality.

▶ Go to: *TGA alert*
Go to: National Asthma Council Australia's *Leukotriene receptor antagonists in the management of childhood asthma* information paper

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### *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.[34]

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.[34]

One small study in adults with acute asthma reported that the addition of oral montelukast to usual care resulted in a slight reduction $beta_2$ agonist requirement,[34] but this difference was clinically nonsignificant.

*Last reviewed version 2.0*

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# 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: http://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.[1] Overall, sodium cromoglycate has not been shown to be effective in preschool children with multiple-trigger wheeze.[1, 2]

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.[3] Sodium cromoglycate is less effective than inhaled corticosteroid in achieving asthma control and improving lung function in children with persistent asthma.[4]

Nedocromil sodium appears to be have some benefit in children with persistent asthma, but its relative effectiveness compared with inhaled corticosteroids is not clear.[5] 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.[6]

### Practical issues

Cromones (sodium cromoglycate and nedocromil) may not be practical for most patients, because they require three–four times daily dosing until control is gained, and inhaler devices for cromones tend to block easily unless the mouthpiece is washed every day and dried for 24 hours before re-use.[3]

Nedocromil can cause an unusual or unpleasant taste[7] and is not tolerated by some children.

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*Cromones for adults and adolescents*

Sodium cromoglycate is less effective than inhaled corticosteroids in controlling asthma and improving lung function.[4]

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[8] and are less effective than short-acting beta$_2$ agonists.[9]

Cromones have a good safety profile and tolerance does not occur when either of these medicines is taken regularly.[8] 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*

*Cromones for 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.[8]

The onset of action is rapid. The duration of action is up to 2 hours.[8]

Recommended doses are as follows:[10]

- 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 beta$_2$ agonists in protecting against exercise-induced bronchoconstriction.[9] However, they have a good safety profile and tolerance does not occur when either of these medicines is taken regularly.[8]

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

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# 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: http://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,[1] 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.[1] 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.[2, 3]

### *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.[4]

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 beta$_2$ agonists.[4] However, significant adverse effects may occur due to recurrent or long-term systemic corticosteroids.[4]

▶ See: *Managing acute asthma in clinical settings*

### *Oral corticosteroids for severe chronic asthma in adults*

In an Australian severe asthma registry study, 24% of patients with severe asthma who had been referred to a severe asthma specialist for assessment were being treated with oral corticosteroids in addition to inhaled corticosteroids and long-acting beta$_2$ agonists.[5]

#### Efficacy

Maintenance treatment with oral corticosteroids for severe asthma has not been evaluated in randomised placebo-controlled trials.[6]

Small randomised trials of intramuscular depot triamcinolone in adults and children with severe asthma, in addition to maintenance or frequent oral corticosteroids, have reported reductions in hospitalisations and emergency department visits, improvement in lung function, and reduced eosinophilic inflammation.[6] However, the use of triamcinolone is associated with more adverse effects than other systemic corticosteroids.

Maintenance treatment with oral corticosteroids should be avoided, if possible, because of the high risk of serious adverse effects.[7, 8, 9]

Monoclonal antibody therapy is one strategy to reduce oral corticosteroid use in adults with severe asthma.[10, 11, 12]

▶ Go to: *National Asthma Council Australia's information paper on Monoclonal antibody therapy for severe asthma*

Other strategies for reducing oral corticosteroid use are being evaluated, such as internet-guided titration based on home monitoring of

symptoms and fraction of exhaled nitric oxide (FeNO).[13]

### Safety

Oral corticosteroid use in adults with asthma is associated with serious adverse events including severe infections, peptic ulcers, affective disorders, cataracts, cardiovascular events including acute myocardial infarction and hypertension, diabetes, fractures and osteoporosis.[14, 15]

Dose–response relationships have been demonstrated for these adverse effects.[14, 15]

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## *Oral corticosteroids for children: adverse effects*

Oral corticosteroids may have adverse psychiatric effects in children, including aggression and hyperactivity.[16] Effects in the general population include euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behaviour.[17]

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.[4] However, risk can accumulate if frequent courses (four or more per year) are given.[4]

Recurrent courses of oral corticosteroids may also affect bone mineral density, especially in boys.[4,18]

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## *Parent/carer-initiated oral corticosteroids for wheezing and asthma flare-ups*

▶ See also: Managing acute asthma in clinical settings

- Oral corticosteroids are associated with adverse effects on behaviour and bone health. Frequent courses may affect the hypothalamus–pituitary–adrenal axis.

### *Children aged 1–5 years*

Short courses of oral corticosteroids initiated by parents/carers in response to children's wheezing, or at the first sign of a cold, are not effective in managing symptoms in preschool children.[19, 20, 21]

There is inconsistent evidence for the benefits of systemic corticosteroids in preschool children with acute viral-induced wheezing presenting to acute care services.[21, 22, 23] Current evidence does not strongly support their use in this age group.[24]

The Thoracic Society of Australia and New Zealand position statement on the use of corticosteroids in children[4] recommends that oral corticosteroid treatment in preschool children, particularly those with intermittent viral-induced wheezing, should be limited to children with wheeze severe enough to need admission to hospital.

### *Children aged 6 years and over*

A Cochrane systematic review found that there was insufficient evidence supporting the use of parent-initiated courses of oral corticosteroids in school-aged children,[25] although some clinical trials have reported benefits.

In a clinical trial in children aged 6–14 years with a history of recurrent episodes of acute asthma, short courses of oral prednisolone (1 mg/kg a day), initiated by parents in response to an asthma flare-ups, reduced asthma symptoms and the number of missed school days.[26] Another quasi-experimental study found that home initiation of corticosteroids reduced the rate of emergency department visits among school-aged children with moderate-to-severe persistent asthma, compared with rates pre-intervention.[27]

The Thoracic Society of Australia and New Zealand position statement on the use of corticosteroids in children[4] recommends a short course of systemic corticosteroid therapy for children with moderate-to-severe acute asthma or when there is an incomplete response to beta-agonists, and does not recommend against parent/carer-initiated courses.

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## *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.[28, 29, 30, 31, 32] A 5-day course of prednisolone 40 mg per day may be as effective as a 10-day course in adults.[30]

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.[28, 31] 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.[33]

*Systemic corticosteroids in acute asthma*

## Systemic corticosteroids in acute asthma

In adults and school-aged children with acute asthma, systemic corticosteroids given within 1 hour of presentation to an emergency department reduce the need for hospital admission.[34] In children admitted to hospital with acute asthma, systemic corticosteroid treatment may achieve earlier discharge and fewer relapses.[35]

In preschool children with acute viral-induced wheezing, there is inconsistent evidence for the benefits of systemic corticosteroids.[36, 37, 38] Oral corticosteroids may be beneficial in children younger than 6 years with frequent acute wheezing or asthma, but current evidence does not strongly support their use in this age group.[39] The Thoracic Society of Australia and New Zealand position statement on the use of corticosteroids in children[4] recommends that the use of systemic corticosteroids in preschool children, particularly those with intermittent viral induced wheezing, should be limited to those with wheeze severe enough to need admission to hospital.

After an acute asthma episode, treatment with systemic corticosteroids (intramuscular corticosteroids, oral prednisone/prednisolone, or oral dexamethasone) at discharge from the emergency department reduces the risk of relapse in adults[40] and children. [41, 42]

## Formulation and route of administration

In adults and children with acute asthma, oral prednisone/prednisolone is as effective as intravenous or intramuscular corticosteroids.[34, 43]

Oral dexamethasone is as effective as prednisone/prednisolone in adults and children[44, 45, 46, 47, 48, 49, 50, 32, 51]

## Dose

In adults, 40 mg per day prednisolone/prednisone,[52] up to 80 mg/day methylprednisolone, or up to 400 mg/day hydrocortisone[53] are adequate.

In children the majority of studies in children have used 1–2 mg/kg of oral prednisolone (maximum 60 mg) given initially then 1 mg/kg per day. Current evidence does not support the use of higher doses.[43]

Studies evaluating oral dexamethasone in adults have used a single dose of 12 mg[44] or 16 mg on 2 consecutive days.[51] Most studies evaluating oral dexamethasone in children have used 0.6 mg/kg per dose on one or two consecutive days.[47]

## Duration

In adults, an oral or intramuscular corticosteroid course of at least 7 days appears more effective than a shorter course in preventing relapse within 10 days of discharge after acute asthma,[40] although one clinical trial evaluating prednisone reported that 5 days was as effective as 10 days.[54] Courses less than 5 days are not recommended.

In children, a 3-day course of prednisone/prednisolone is generally as effective as a 5-day course,[55] but 5 days may be needed for children with severe or life-threatening acute asthma.[4]

It is not necessary to taper the dose after a short course of oral prednisone/prednisolone.[4028, 56]

Dexamethasone has a longer half-life than prednisone/prednisolone. Longer courses may more pronounced mineralocorticoid adverse effects. Oral dexamethasone treatment in adults or children should not exceed 2 days.

## Adverse effects

Short-term use of oral corticosteroids to treat acute asthma is often well tolerated in children and adults,[34, 35, 37, 32] but many patients report significant adverse effects, particularly mood changes, gastrointestinal disturbances,[56] nocturia, and difficulty sleeping. While short courses of high-dose systemic treatment cause fewer adverse effects than prolonged courses of lower doses,[57] more recent analyses have shown a significant association between short courses of oral corticosteroids and sepsis, thromboembolism and fracture.[58, 59]

Oral dexamethasone appears to be well tolerated in adults.[44] In children it may be associated with less vomiting than prednisone/prednisolone.[45, 46, 47, 48, 49, 50] The risk of unwanted mineralocorticoid effects are increased if dexamethasone is taken for more than 2 days.

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.

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### *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.[60] 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.[60]

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,[61] 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.[60] These adverse effects can occur in people without a previous history of psychiatric illness.[60]

Systemic corticosteroid treatment has been associated with elevated mood and reduction in depression among patients with asthma.[62, 63] With long-term prednisone or prednisolone therapy, initial mood changes appear to stabilise over time.[64]

### *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.[65, 66]

If high-dose corticosteroids need to be used for longer than 10 days, the infant should be monitored for growth and development.[65, 66]

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)

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# 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 or severe acute asthma. They include:

- anti-IgE (omalizumab)
- anti-IL5 (mepolizumab) and anti-IL5 receptor (benralizumab)
- long-acting muscarinic antagonists; also called long-acting anticholinergic bronchodilators (tiotropium via mist inhaler)
- magnesium sulfate
- theophyllines (aminophylline, theophylline).

Some additional long-acting bronchodilator medications are TGA-approved only for management of COPD, but might be used in addition to inhaled corticosteroid-containing therapy for the treatment of patients with asthma–COPD overlap. These include:

- long-acting muscarinic antagonists; also called long-acting anticholinergic bronchodilators (aclidinium, glycopyrronium, tiotropium via dry-powder inhaler, umeclidinium)
- long-acting beta2 agonists (e.g. vilanterol in combination with inhaled corticosteroid or long-acting muscarinic antagonist).

**Note:** The use of separate inhalers for concomitant treatment with an inhaled corticosteroid and a long-acting bronchodilator (long-acting beta$_2$-agonist or long-acting muscarinic antagonist) in patients with asthma–COPD overlap should be avoided due to the risk of selective non-adherence with the inhaled corticosteroid. If no combination product is available for the desired combination, carefully explain to the patient that it is very important that they continue taking the inhaled corticosteroid, to reduce the risk of hospitalisation or death.

*Table. Classification of asthma medicines*

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

*Table. Long-acting bronchodilators for asthma–COPD overlap*

| *Class* | *Dosing frequency* | *Agent* | **Brand name** |
|---|---|---|---|
| *ICS–LABA combinations* | Once daily | Fluticasone furoate + vilanterol | *Breo Ellipta 100/25 microg*[†]<br>• Do not prescribe 200/25 microg formulation[#] |
| | Twice daily | Budesonide + formoterol | *Symbicort Rapihaler*<br>*Symbicort Turbuhaler* |
| | Twice daily | Fluticasone propionate + formoterol | *Flutiform* |
| | Twice daily | Fluticasone propionate + salmeterol | *Fluticasone and Salmeterol Cipla*<br>*Seretide Accuhaler* |

| *Class* | *Dosing frequency* | *Agent* | **Brand name** |
|---|---|---|---|
| | | | *Seretide MDI* |
| *LABAs** | Once daily | Indacaterol | *Onbrez Breezhaler* |
| | Twice daily | Formoterol | *Oxis*<br>*Foradile* |
| | Twice daily | Salmeterol | *Serevent Accuhaler* |
| *LAMAs** | Once daily | Glycopyrronium | *Seebri Breezhaler* |
| | Once daily | Tiotropium | *Spiriva*<br>*Spiriva Respimat* |
| | Once daily | Umeclidinium | *Incruse Ellipta*‡ |
| | Twice daily | Aclidinium | *Bretaris Genuair* |
| *LABA–LAMA combinations** | Once daily | Indacaterol + glycopyrronium | *Ultibro Breezhaler* |
| | Once daily | Olodaterol + tiotropium | *Spiolto Respimat* |
| | Once daily | Vilanterol + umeclidinium | *Anoro Ellipta*‡ |
| | Twice daily | Formoterol + aclidinium | *Brimica Genuair* |

- * Ensure that patient is also using regular long-term ICS. LABAs and LAMAs should not be used by people with asthma or asthma–COPD overlap unless they are also taking an ICS, in combination or separately)
- Advise patients/carers that inhalers should be stored below 30°C and should not be left in cars.

† The inhaler must be discarded 1 month after opening the package and removing device from tray. When first opened, patients should write the discard date on the label in the space provided. If stored in the refrigerator, inhaler should be taken out and allowed to return to room temperature for at least an hour before use.

‡ The inhaler must be discarded 6 weeks after opening after opening the package and removing device from tray. When first opened, patients should write the discard date on the label in the space provided. If stored in the refrigerator, inhaler should be taken out and allowed to return to room temperature for at least an hour before use.

# Only the 100/25 microg dose of fluticasone furoate/vilanterol is TGA-approved for treatment of COPD. The higher dose (200/25 microg) is not TGA-approved for the treatment of COPD, so it should not be used in people with asthma–COPD overlap.

High doses of ICS (alone or in combination) are not recommended in patients with COPD and should therefore be used with caution in patients with asthma-COPD overlap, because of the risk of pneumonia.

Refer to PBS status before prescribing.

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## More information

### *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).[1]

▶ 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.[2]

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

▶ See: *Managing acute asthma in clinical settings*

### *Tiotropium for children aged 6 years and over*

Tiotropium (5 microg administered via mist inhaler as two puffs once daily) is approved by TGA for use in children aged 6 years and older with moderate-to-severe asthma.

Tiotropium is subsidised by then PBS for children aged 6–17 years when used in combination with maintenance ICS+LABA treatment, for patients with severe asthma treated by, or in consultation with, a specialist (respiratory physician, paediatric respiratory physician, clinical immunologist, allergist, paediatrician or general physician experienced in severe asthma management), with frequent moderate exacerbations or ≥ one documented severe exacerbation that required systemic corticosteroids in the previous 12 months despite maintenance treatment with a medium-to-high dose of inhaled corticosteroid in combination with a long-acting beta2 agonist, and correct inhaler technique has been assessed, demonstrated and documented (see PBS for details).

▶ Go to: *PBS listings*

#### *Children aged 6–11*

A systematic review of three randomised controlled trials reported that, in children aged 6–11 years with moderate-to-severe symptomatic asthma, tiotropium improved lung function, improved symptoms, and reduced the rate of flare-ups.[3] Tiotropium was generally well tolerated.[3]

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### *Tiotropium for adults and adolescents*

**Tiotropium via mist inhaler (not dry-powder inhaler) is approved by the TGA for add-on maintenance treatment in patients with moderate-to-severe asthma.**[4]

Tiotropium is well tolerated.[5, 6]

**Note**: PBS status as at March 2019:

Adults: Tiotropium is subsidised by the PBS for use in combination with a maintenance combination of an inhaled corticosteroid and a long acting beta$_2$ agonist for patients with severe asthma who have had at least one severe flare-up in the previous 12 months that required documented systemic corticosteroids, while receiving optimised asthma therapy with a combination of at least 800 mg budesonide per day or equivalent and a long acting beta$_2$ agonist, and correct inhaler technique has been assessed, demonstrated and documented.

Children and adolescents aged 6–17 years: Tiotropium is subsidised by the PBS for use in combination with a maintenance combination of an inhaled corticosteroid and a long acting beta2 agonist for patients with severe asthma who have had at least one severe flare-up in the previous 12 months that required documented systemic corticosteroids, while receiving optimised asthma therapy with a combination of a medium-to-high dose of an inhaled corticosteroid and a long acting beta2 agonist, and correct inhaler technique has been assessed, demonstrated and documented.

▶ Go to: *PBS listings*

#### Adults

#### Tiotropium added to inhaled corticosteroid therapy

A Cochrane review and meta-analysis 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.[7]

Another systematic review and meta-analysis of long-acting muscarinic antagonists (tiotropium or umeclidinium) in patients with poorly controlled asthma despite taking inhaled corticosteroids reported that the addition of a long-acting muscarinic antagonist significantly reduced the risk of an asthma flare-up requiring systemic corticosteroids, or of asthma worsening, compared with placebo.[8] There were no significant effects on asthma control, reliever use or quality of life.[8] In most included studies participants were adults with a mean age between 30 and 40 years.[8]

However, there is insufficient evidence overall to support the use of tiotropium as an alternative to a long-acting beta$_2$ agonist as add-on therapy. In contrast, there is a large evidence base supporting the combination of inhaled corticosteroid and long-acting beta$_2$ agonist in adults.

### Tiotropium versus long-acting beta$_2$ agonist added to inhaled corticosteroids

Few studies have compared tiotropium with long-acting beta$_2$ agonists as add-on therapy in patients taking inhaled corticosteroids. Direct evidence is mainly limited to studies of less than 6 months' duration comparing tiotropium with salmeterol. Meta-analysis of these studies showed no significant difference between treatment groups in flare-ups requiring oral corticosteroids, lung function, symptom control or asthma-related quality of life.[8]

While there is insufficient evidence to support the use of tiotropium as an alternative to a long-acting beta$_2$ agonist as add-on therapy in patients taking an inhaled corticosteroid, it may be a suitable alternative for patients who have experienced adverse effects of long-acting beta$_2$ agonist therapy.

### Tiotropium added to the combination of inhaled corticosteroid and long-acting beta$_2$ agonist

The addition of tiotropium bromide via mist inhaler therapy is effective in improving lung function and reducing worsening asthma in adults and adolescents with asthma that is uncontrolled despite taking a combination of inhaled corticosteroid and long-acting beta$_2$ agonist, but does not reduce the rate of severe flare-ups requiring oral corticosteroid.[8]

A Cochrane review[9] 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 oral corticosteroids in adults with severe asthma.

Another systematic review and meta-analysis found that the addition of a long-acting muscarinic antagonist (tiotropium or umeclidinium) to the combination an inhaled corticosteroid and a long-acting beta$_2$ agonist in adults significantly reduced the rate of worsening asthma, but not the rate of severe flare-ups requiring oral corticosteroids, and had no significant effect on other outcomes including lung function or symptom control.[8]

### Adolescents

### Tiotropium added to inhaled corticosteroid therapy

A meta-analysis of randomised placebo-controlled clinical trials in adolescents 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.[6] In those with poorly controlled asthma despite treatment with medium-to-high doses of inhaled corticosteroids, tiotropium was not inferior to salmeterol.[6]

Another systematic review and meta-analysis of clinical trials of long-acting muscarinic antagonists in patients with poorly controlled asthma included only two trials evaluating tiotropium in adolescents aged 12–17 years. Tiotropium added to inhaled corticosteroid treatment was associated with numerical improvements in lung function, but this reached significance in comparison with placebo in only one study. Both studies in adolescents reported large placebo effects, which may have been due to improved adherence to inhaled corticosteroids during the trial.[8]

### Tiotropium added to the combination of inhaled corticosteroid and long-acting beta$_2$ agonist

A meta-analysis of randomised placebo-controlled clinical trials in adolescents with asthma reported that, among 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.[6]

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## *Monoclonal antibody therapy for severe asthma*

Three monoclonal antibody therapies (omalizumab, mepolizumab and benralizumab) are available in Australia for the treatment of patients with severe asthma whose asthma is uncontrolled despite optimised standard treatment including high-dose inhaled corticosteroids and long-acting beta$_2$ agonists.

**Table. Monoclonal antibody therapies currently available in Australia for severe asthma**

| Name | Description | Indication* | Dosage & route of |
|---|---|---|---|

SC: subcutaneous

**Refer to TGA-approved indications and PBS criteria*

▶ Go to: *TGA product information*

▶ Go to: *PBS medicine listing*

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Monoclonal antibody therapy reduces the rate of severe flare-ups requiring systemic corticosteroids. [REFERENCE226], 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 Many patients also experience improvement in asthma symptoms[10, 11, 13, 14, 15, 17, 20, 21, 22] and quality of life.[10, 15, 16, 23] Some studies have also shown a reduction in oral corticosteroid in patients with severe asthma.[10, 11, 24, 15, 19, 20]

These therapies are generally well tolerated.[10, 13, 14, 18, 25] Injection site reactions are among the most common adverse events. Systemic reactions, including anaphylaxis, are rare but can occur.[26]

Monoclonal antibody therapies are funded by PBS only when prescribed by specialists (respiratory physician, clinical immunologist, allergist or general physician or paediatrician experienced in severe asthma management), for patients attending a public or private hospital, and when patients meet certain general and product-specific criteria. After treatment is initiated by a specialist, ongoing maintenance doses can be administered in primary care, but regular review for continuing PBS-funded treatment must be carried out by the specialist.

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### *Azithromycin for moderate-to-severe-asthma*

Macrolide antibiotics have both anti-inflammatory effects and antimicrobial effects. Azithromycin and clarithromycin are used in the management of cystic fibrosis,[27] bronchiectasis[28] and COPD[29] to reduce exacerbation rates.

#### Efficacy in asthma

The role of macrolides in the treatment of severe asthma is uncertain.[29, 30] The long-term use of azithromycin in adults with severe asthma may reduce flare-ups and improve symptom control, based on limited evidence.[5]

An Australian placebo-controlled randomised controlled trial reported that 48 weeks' treatment with azithromycin 500 mg three times weekly reduced flare-ups and improved quality of life in adults with symptomatic asthma despite treatment with a moderate or high dose of inhaled corticosteroid and long-acting bronchodilator.[31] Although long-term macrolide therapy was initially expected to be of most benefit patients with neutrophilic asthma, in this study a significant reduction in exacerbations was seen both in patients with eosinophilic and those with non-eosinophilic asthma. The greatest benefit was in those with positive bacterial culture. The study reported a nonsignificant increase in azithromycin-resistant organisms in sputum of patients treated with azithromycin, compared with placebo, but it was not adequately powered to fully assess this effect.

An earlier 6-month placebo-controlled randomised controlled trial in patients with severe asthma reported that low-dose azithromycin added to inhaled corticosteroids and long-acting beta$_2$ agonist improved quality of life, but did not reduce the rate of severe flare-ups, improve asthma control or improve lung function.[24] However, among the subgroup of patients with non-eosinophilic severe asthma, azithromycin significantly reduced the rate of a combined endpoint of either severe flare-ups or lower respiratory tract infections requiring antibiotics.[24] Azithromycin was associated with an increased rate of oropharyngeal carriage of macrolide-resistant streptococci.[24]

Compared with standard doses for infections, macrolide doses evaluated in studies of long-term asthma treatment are generally lower.

The evidence for the use of macrolides in children and adolescents with severe asthma is limited and inconclusive due to a lack of completed trials.[5]

#### Safety

Although azithromycin is generally well tolerated, rare adverse effects include QTc prolongation and hearing impairment.[32, 31] Patients with either of these problems were excluded from the randomised controlled trials assessing the use of azithromycin in the treatment of moderate-to-severe or severe asthma.[24]

There are also concerns about the potential for development of resistance. Specialist advice is recommended, including consultation with a local infectious diseases expert, before prescribing macrolides for asthma.

Atypical mycobacterial infections, hearing impairment and prolonged QT interval should be ruled out before prescribing. Treatment-related adverse effects should be monitored by ECG, audiology and liver function tests.

**Note**: Azithromycin and clarithromycin are not registered by the TGA for the long-term treatment of asthma.

**Note**: Azithromycin is not subsidised by the PBS for long-term use.

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*Ipratropium in acute asthma*

### Adults

In adults and older adolescents with severe acute asthma treated in the emergency department, the combination of ipratropium and short-acting beta$_2$ agonist reduces hospitalisation rate and improves lung function, compared with short-acting beta$_2$ agonist alone.[33] Hospitalisation rates are not reduced in patients with mild or moderate acute asthma.[33]

In adults, the combination of ipratropium and short-acting beta$_2$ agonist is associated with a higher rate of adverse effects (e.g. tremor, agitation, and palpitations) than short-acting beta$_2$ agonist alone.[33]

### Children

Recent systematic reviews have reported that initial treatment with ipratropium in addition to salbutamol markedly reduces hospitalisation rate and improves clinical scores in children with moderate to severe acute asthma.[34, [REFERENCE1907], 36]

However, in children hospitalised due to acute asthma, the combination of ipratropium and short-acting beta$_2$ agonist was not more effective than short-acting beta$_2$ agonist alone.[37]

The combination of ipratropium and short-acting beta$_2$ agonist appears to be well tolerated in children.[36]

Ipratropium bromide alone is less effective than salbutamol alone in acute asthma.[38]

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*Magnesium sulfate in acute asthma*

### Magnesium sulfate in acute asthma

Clinical trial evidence does not support the use of magnesium sulfate as a substitute for inhaled beta$_2$ agonists.[39]

Its main use is in addition to salbutamol, either in combination with initial bronchodilator treatment, or as an add-on treatment in patients with inadequate response to initial bronchodilator treatment.

### Intravenous magnesium sulfate

### Adults

IV magnesium sulfate may have a small effect in reducing hospital admissions and may improve lung function in adults with acute asthma who have failed to respond to standard treatment.[40, 41]

In a 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), IV magnesium sulfate improved dyspnoea scores but did not reduce hospital admission rates.[42]

Current evidence does not indicated whether or not IV magnesium sulfate is more effective for patients with a more severe acute asthma.[40]

The optimal dose and infusion regimen has not been identified.[40]

IV magnesium sulfate IV appears to be well tolerated in adults.[40] Minor flushing is the most common adverse event.[40] Other adverse effects reported in clinical trials include fatigue, nausea, headache and hypotension.[41]

### Children

IV magnesium sulfate may reduce hospitalisation rates and improve lung function among children with acute asthma in presenting to the emergency department,[43, 44] but there is limited evidence.[44]

A small randomised controlled trial reported that IV magnesium sulfate was ineffective in reducing respiratory distress in very young children (6 months to 4 years) with acute virus-induced wheezing.[45]

IV magnesium sulfate is generally well tolerated.[44, 46]

### Nebulised magnesium sulfate

Nebulised magnesium sulfate may achieve small additional improvement in lung function and reduction in hospital admission rates

when added to salbutamol and ipratropium in adults and children with acute asthma, but these benefits have not been clearly demonstrated on current evidence.[39]

Randomised controlled trials have reported conflicting findings. The larger and more recent studies typically show a smaller effect than some of the older, smaller studies.[39] Large, well-designed trials in adults[42] and children[47, 48, 49] have generally not demonstrated clinically important benefits.[39] A systematic review of randomised controlled trials found no overall improvement in lung function when magnesium sulfate was added to salbutamol and ipratropium.[39]

Nebulised magnesium sulfate is well tolerated and does not appear to be associated with an increase in serious adverse events.[39]

### Adults

It is uncertain whether nebulised magnesium sulfate improves lung function or symptoms, or reduces hospital admissions, when added to standard treatment in adults.[40]

Some studies suggest that patients presenting with severe acute asthma may benefit, but the data are not conclusive.[40]

A large, well-designed RCT showed no reduction in hospitalisation or dyspnoea rates in adults with acute asthma given add-on nebulised magnesium, compared with standard therapy alone,[42, 50] but this study excluded patients with life-threatening acute asthma.

### Children

A recent systematic review found that nebulised magnesium sulfate had no effect on hospitalisation rates or lung function in children with acute asthma.[43]

However, one large, well-designed randomised controlled trial in children reported that 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 ($SaO_2$<92%), and those with more sudden onset (symptoms less than 6 hours before acute attack).[47, 48]

Nebulised magnesium sulfate is well tolerated in children.[47, 48]

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## *Theophyllines in acute asthma*

Few studies have compared IV aminophylline with IV short-acting $beta_2$ agonist in the management of acute asthma in adults and children.

Compared with salbutamol IV aminophylline is associated with a higher rate of adverse effects including giddiness, nausea and vomiting.[51]

It is used mainly as an add-on therapy when there is inadequate response to initial bronchodilator.

### Aminophylline plus salbutamol in 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 $beta_2$ agonists does not achieve greater bronchodilation or reduce hospital admissions, compared with inhaled $beta_2$ agonists alone.[52] No sub-groups that benefit from intravenous aminophylline have been clearly identified.[52]

Aminophylline is associated with vomiting and cardiac arrhythmias.[52]

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.[53]

### Aminophylline plus salbutamol in children

In children with acute asthma requiring hospital admission, the addition of intravenous aminophylline to $beta_2$-agonists and corticosteroids (with or without ipratropium) may improve lung function within 6 hours of treatment, but does not appear to improve symptoms or shorten hospital stay.[54]

The optimal aminophylline dose in children has not been clearly identified. Evidence from clinical trials does not show a clear association between dose and clinical outcomes.[55]

Aminophylline is associated with a significant increased risk of vomiting in children.[54] The rate of adverse effects appears to be higher among children receiving higher loading doses of IV aminophylline (7–10 mg/kg), compared with 5–6 mg/kg.[55]

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## *Roles of adrenaline in the management of acute asthma*

Adrenaline is not used routinely in the management of severe acute asthma.

Its use should be reserved for situations where inhaled salbutamol cannot be given in a patient with respiratory arrest or pre-arrest status, or when anaphylaxis is suspected.

## Anaphylaxis

Anaphylaxis is rare among people with acute asthma. An estimated 3.4% of adults admitted to the intensive care unit for acute severe asthma also meet criteria for anaphylaxis, according to one retrospective study.[56]

Intramuscular adrenaline (or intravenous adrenaline in clinical settings with appropriately trained staff) is indicated for patients with anaphylaxis and angioedema, and patients with known allergies to food or other relevant allergens (other than aeroallergens) who have sudden-onset breathing problems, even if they have no other signs of anaphylaxis.[57]

Australasian Society of Clinical Immunology and Allergy recommends that adrenaline should be given before bronchodilators for a patient with sudden-onset breathing problems and known allergy to foods, insects or medicines.[57]

▶ Go to: Australasian Society of Clinical Immunology and Allergy (ASCIA)'s *guidelines on acute management of anaphylaxis*

## Asthma

Few studies have compared adrenaline in addition to, or in comparison with, currently recommended bronchodilator treatment in patients with acute asthma, either in hospital emergency departments or pre-hospital acute services.

### *Hospital or emergency department setting*

*Nebulised adrenaline*
Nebulised adrenaline does not have a significant benefit over salbutamol or terbutaline in the management of moderate-to-severe acute asthma in adults and children.[58]

*Intramuscular, intravenous or subcutaneous adrenaline*
Adrenaline given IV, subcutaneously or intramuscularly has no benefit over inhaled short-acting beta$_2$ agonists in the management of acute asthma.[59, 60, 61, 62]

Three small clinical trials comparing subcutaneous adrenaline with nebulised salbutamol in children with acute asthma reported equivalent respiratory outcomes including peak expiratory flow rate.[59, 60, 61] Adrenaline was associated with higher rates of adverse effects, including a short-term increase in systolic blood pressure and heart rate.[59, 60]

Another trial in children with acute asthma reported that subcutaneous adrenaline was more effective than nebulised terbutaline in increasing oxygen saturation and $FEV_1$, but was associated with a higher rate of adverse events including pallor, tremor, dizziness, headache, palpitation, soreness of legs, numbness of extremities, cold sweating, general weakness and nausea.[63]

A clinical trial comparing subcutaneous adrenaline with nebulised terbutaline in adults with acute asthma reported equivalent efficacy.[62] The adrenaline group, but not the terbutaline group, showed an increase in pulse rate.[62] A non-comparative retrospective study of 220 adults who had received IV adrenaline for acute asthma reported that adverse events were common but mostly minor and self-limiting.[64] Major adverse events occurred in approximately 4% of patients and included 2 cases of supraventricular tachycardia, 1 case of chest pain with ECG changes, 1 case of incidental elevated troponin, and 4 cases of hypotension requiring intervention.[64]

### *Prehospital setting*

There is limited evidence to guide the use of adrenaline in patients with acute asthma in the prehospital setting. However, it has no benefit over inhaled salbutamol in patients with acute asthma and is associated with a worse adverse effect profile.

Subcutaneous adrenaline was associated with increased heart rate and increased blood pressure, compared with a nebulised bronchodilator (metaproterenol), in a randomised controlled trial in adults presenting to ambulance services with acute asthma.[65]

In some states, ambulance services give adrenaline to patients with severe, life-threatening acute asthma. In this circumstance inhaled/nebulised salbutamol is preferable initially. When there is an inadequate response with acute and rapid deterioration or when the inhaled route is impractical because the person is not breathing, some ambulance protocols recommend administration of either IM Adrenaline (500 mg, 1:1000), if needed at intervals of 5–10 minutes or IV adrenaline 50–100 mg at intervals of 2–5 minutes.[66]

Ventilation must be adequately supported. If cardiac or respiratory arrest occurs, appropriate resuscitation procedures should be followed.[67]

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### *Role of ketamine in acute asthma*

Ketamine has been proposed by some researchers as a suitable option for pre-intubation sedation in patients with respiratory failure caused by acute asthma (where not contraindicated) because it stimulates the release of catecholamines and may contribute to bronchodilation through direct relaxation effect on bronchial smooth muscle.[68]

Evidence does not strongly support the use of ketamine in non-intubated children with acute asthma.[69] The results of small studies suggest that ketamine at a dose of approximately 1 mg/kg may have some benefit in bronchodilation and clinical symptoms in

children.[70] However, benefits compared with other add-on treatments for acute asthma and long-term effects have not been established.[70] In children with acute asthma who have an inadequate response to initial bronchodilator therapy, the effect of IV ketamine on respiratory status may be equivalent to that to that of IV aminophylline.[71]

Adverse effects associated with ketamine include hypersecretion, hypotension and hypertension, arrhythmias, and hallucinations.[68]

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### *Antibiotics in acute asthma*

Antibiotics are not used routinely in the management of acute asthma but should be used if they would otherwise be indicated.

The role of atypical bacterial infections (e.g. *Chlamydophyla pneumonia*, *Mycoplasma pneumonae*) in asthma is under investigation. Atypical bacterial infections may make acute asthma more severe, especially in patients with poorly controlled asthma. Macrolide antibiotics are active against atypical bacteria and have anti-inflammatory activity. However, their potential anti-inflammatory effects in the treatment of acute asthma have not been well studied.

A systematic review[72] of antibiotic treatment in asthma flare-ups found that the few available randomised controlled trials were heterogeneous and that their findings were inconsistent. It concluded that there was limited evidence that antibiotics given at the time of an asthma flare-up may improve symptoms and lung function at follow-up, compared with standard care or placebo.[72]

The systematic review identified four studies that assessed the use of macrolide antibiotics in the management of asthma flare-ups. Combined results for two of these (416 participants) showed that macrolide treatment was associated with improvement in symptoms.[72] One included study reported an increase in symptoms-free days at 10 days in adults treated with a macrolide, compared with placebo, which was independent of serological evidence for infection with chlamydia pneumonia or mycoplasma pneumoniae. However, the study drug (telithromycin) is no longer in use due to its association with severe liver toxicity.

In a study of adults attending emergency care for acute asthma, treatment with azithromycin 500 mg per day for 3 days was not associated with an improvement in symptoms or lung function, compared with placebo.[73] However, 1 in 10 participants assessed for this trial were excluded as they had already commenced an antibiotic at the time of screening.

In a study of children aged 1–5 years presenting to the emergency department with acute wheezing illness,[74] children were randomised to either azithromycin for 5 days or placebo. Azithromycin treatment did not reduce the duration of respiratory symptoms or the time to a respiratory flare-up in the following 6 months after treatment.[74]

A small (n=40) study assessing clarithromycin treatment in children aged 1–3 years with acute wheezing illness reported an increase in symptoms-free days at 3, 6 and 12 weeks, compared with usual care.[75]

The systematic review of antibiotic treatment in asthma flare-ups[72] included two studies investigating penicillin treatment in patients admitted to hospital with asthma. Neither observed a significant difference in duration of admission, and one reported no difference in asthma symptoms at discharge.[72]

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# 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*

# Tools for primary care

## In this section

# Asthma action plans

Every person with asthma should have their own written asthma action plan that is appropriate for their treatment regimen, asthma severity, culture, language, literacy level, and ability to self-manage.

When provided with appropriate self-management education, self-monitoring and medical review, individualised written action plans consistently improve asthma health outcomes.

The National Asthma Council Australia has a range of asthma action plan templates available to order or download:

▶ Go to: *Asthma action plans*

Go to: *Asthma action plan library*

Go to: *Translated action plans*

# Asthma control questionnaires

Questionnaire-based tools can be used to standardise review of asthma symptoms.

## *Asthma Score (Asthma Control Test)*

The Asthma Score is a questionnaire-based tool that can be used to standardise review of asthma symptoms.



*Table. Asthma Score*

**Please view and print this figure separately: http://www.asthmahandbook.org.au/table/show/88**

*Table. Interpretation of Asthma Score (Asthma Control Test)*

| Score | Interpretation |
|---|---|
| ≥ 20 | Well-controlled asthma |
| ≤ 15 | Uncontrolled asthma |
| Change of ≥ 3 points | Clinically important change in an individual patient |

*Sources*

Schatz M, Sorkness CA, Li JT *et al*. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol* 2006; 117: 549-56. Available from: http://www.jacionline.org/article/S0091-6749(06)00174-6/fulltext

Schatz M, Kosinski M, Yarlas AS *et al*. The minimally important difference of the Asthma Control Test. *J Allergy Clin Immunol* 2009; 124: 719-23. Available from: http://www.jacionline.org/article/S0091-6749(09)01245-7/fulltext

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## *Primary care Asthma Control Screening tool (also known as Pharmacy Asthma Control Screening tool)*

A quick screening test to detect poor asthma control, developed and validated for use with Australian patients attending primary care

*Table. Primary care Asthma Control Screening tool (PACS)*

| Have you experienced any of the following more than once a week in the last month? | Yes | No |
|---|---|---|
| Symptoms of asthma, cough, wheeze, shortness of breath | • | • |
| Waking at night because of asthma | • | • |
| Chest tightness on waking | • | • |

**Interpretation:** 'Yes' to any question indicates that the person may have poorly controlled asthma, so more detailed assessment is needed.

*Source:* LeMay KS, Armour CL, Reddel HK. Performance of a brief asthma control screening tool in community pharmacy: a cross-sectional and prospective longitudinal analysis. *Prim Care Respir J*; 2014. Available from: http://dx.doi.org/10.4104/pcrj.2014.00011

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### *UK Royal College of Physicians '3 Questions' screening tool*

*Table. UK Royal College of Physicians '3 Questions' screening tool*

| **In the last month:** | **Yes** | **No** |
|---|---|---|
| Have you had difficulty sleeping because of your asthma symptoms (including cough)? | • | • |
| Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)? | • | • |
| Has your asthma interfered with your usual activities (e.g. housework, work/school etc)? | • | • |

**Inerpetation:**

No to all three questions indicates good control.

Yes to 2 or 3 questions indicates poor control.

Yes to 1 question indicates that more detailed questioning is needed to assess level of asthma control (using another validated questionnaire or by asking about frequency of daytime symptoms, reliever requirement, limitation of activities and symptoms at night or on waking during the previous month).

**Note**: This test provides a quick and easy way of confirming someone's asthma control is good, or identifying those who need more assessments.

*Sources*

Thomas M, Gruffydd-Jones K, Stonham C *et al.* Assessing asthma control in routine clinical practice: use of the Royal College of Physicians '3 Questions'. *Prim Care Respir J* 2009; 18: 83-8. Available from: http://www.nature.com/articles/pcrj200845

Pinnock H, Burton C, Campbell S *et al.* Clinical implications of the Royal College of Physicians three questions in routine asthma care: a real-life validation study. *Prim Care Respir J* 2012; 21: 288-94. Available from: http://www.nature.com/articles/pcrj201252

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### *Asthma Control Questionnaire (ACQ)*

▶ Go to: *Asthma Control Questionnaire (ACQ)*

**Note:** Clinicians and researchers should only use the versions of the ACQ and Asthma Score that have been validated for use in the Australian population. The wording and layout of questionnaires must not be changed.

# First aid instructions for patients, parents and community members

First aid instructions for patients, parents and community members are available from the National Asthma Council Australia.

The first aid instructions are available as charts for use with all patients or for use with children up to 12 years:

- First aid for asthma
- Kids' first aid for asthma

▶ Go to: National Asthma Council Australia's *first aid charts*

# Inhaler technique videos

Incorrect use of inhalers may lead to insufficient drug delivery to the airways, and is associated with worse asthma control. However, the majority of patients do not use inhaler devices correctly.

Instructional 'How-to' videos demonstrating correct technique can help ensure patients are using their inhalers correctly.

National Asthma Council Australia's very popular 'How-to' videos cover a range of inhaler devices used with asthma and COPD medicines, plus common intranasal corticosteroid sprays.

NPS MedicineWise also has resources to support correct use of inhaler devices.

▶ Go to: National Asthma Council Australia's *How-to video library*
Go to: NPS MedicineWise's information on *Inhaler devices for respiratory medicines*

# Peak flow chart for monitoring expiratory flow

Due to the wide range of 'normal' values and high degree of variability, peak expiratory flow is not the recommended test to identify asthma. However, it can be useful in some circumstances.

A small proportion of people with asthma may benefit from regular peak flow monitoring. When monitoring is recommended, it is usually done in addition to reviewing asthma symptoms and frequency of reliever medication use.

Peak flow measurements are most useful if they are displayed on a chart or graph rather than just written down as a list. The *Woolcock Institute of Medical Research* has developed a standardised and user-friendly peak flow chart so primary carers and patients can monitor symptoms together.

▶ Go to: National Asthma Council Australia's *Information on peak flow and standardised chart*

# Spirometry resources

Spirometry is the best lung function test for diagnosing asthma and for measuring lung function when assessing asthma control. The measurement of peak expiratory flow with conventional peak flow meters has significant limitations.

From education workshops to spirometer buyers' guides, National Asthma Council Australia has a range of tools and other resources to help health professionals with this all-important aspect of asthma diagnosis and monitoring.

▶ Go to: National Asthma Council Australia's *Spirometry resources*

# Resources for patients

## In this section

# My Asthma Guide: the Handbook for patients

*My Asthma Guide: My Handbook for Managing Asthma* translates the most important information from the *Australian Asthma Handbook* into an easy-to-understand summary for people with asthma and their families.

Finding the balance between practical advice and the best evidence, *My Asthma Guide* is the perfect resource for patients recently diagnosed with asthma (or their caregivers) or for patients interested in gaining a better understanding of their asthma.

*My Asthma Guide* is published in full on the National Asthma Council Australia website. Free printed copies are also available.

▶ Go to: *My Asthma Guide*

# Education and support for patients and their families

Australia is fortunate to have a range of professional organisations that can provide expert advice to patients on asthma, allergy, COPD and other lung or respiratory conditions.

### *National Asthma Council Australia*

The National Asthma Council Australia is Australia's lead asthma authority. While well-known and respected for its high quality asthma education and resources for health professionals, including this Handbook, the Council also provides a range of resources for people with asthma including How-to videos and factsheets.

▶ *National Asthma Council Australia*

### *Asthma Australia and the state-based Asthma Foundations*

Asthma Australia is the national body representing all the State-based asthma foundations in Australia and the peak advocacy body for Australians with asthma. Asthma Australia and the Foundations provide a range of resources and other services for patients and their carers.

Information line: 1800 ASTHMA

▶ *Asthma Australia* (including the Asthma Foundations of ACT, New South Wales, Northern Territory, Queensland and South Australia)
*Asthma Foundation of Tasmania*
*Asthma Foundation of Victoria*
*Asthma Foundation of Western Australia*

### *Lung Foundation Australia*

The Lung Foundation Australia supports all aspects of lung health, particularly COPD, based around the tenets of advocacy, awareness and education. It provides a range of excellent resources and programs for patients.

▶ *Lung Foundation Australia*

### *Australasian Society of Clinical Immunology and Allergy (ASCIA)*

ASCIA is the peak professional medical organisation for allergy and clinical immunology in Australia and New Zealand. ASCIA has a range of patient resources for people with allergic diseases including factsheets and online training.

▶ *Australasian Society of Clinical Immunology and Allergy (ASCIA)*

### *NPS MedicineWise*

NPS (National Prescribing Service) MedicineWise has reliable and independent health and treatment information about a range of respiratory conditions. It has many patient resources for people with asthma and their families.

▶ *NPS MedicineWise*

### *Healthdirect Australia*

Healthdirect has health information that is easy to understand and simple to follow. Its pages link to related content from trusted organisations and peak bodies, to help guide consumers to quality Australian content.

▶ *Healthdirect Australia*

# Definitions and commonly used terms

## A working definition of asthma

Asthma is a chronic lung disease, which can be controlled but not cured.

In clinical practice, asthma is defined by the presence of **both** the following:

- excessive variation in lung function ('variable airflow limitation', i.e. variation in expiratory airflow that is greater than that seen in healthy people)
- respiratory symptoms (e.g. wheeze, shortness of breath, cough, chest tightness) that vary over time and may be present or absent at any point in time.

In young children in whom lung function testing is not feasible, including most preschool children, asthma is defined by the presence of variable respiratory symptoms.

Untreated asthma is usually characterised by chronic inflammation involving many cells and cellular elements,[1] airway hyperresponsiveness,[1] and intermittent airway narrowing (due to bronchoconstriction, congestion or oedema of bronchial mucosa, mucus, or a combination of these).

Asthma probably represents a spectrum of conditions with different pathophysiological mechanisms.[2] In older patients, there may be substantial overlap with the features of COPD.

The diagnosis of allergic asthma is more likely when the person also has allergy and a family history of asthma.

**Notes**

To confirm the diagnosis of asthma, it is necessary to demonstrate excessive variation in lung function, i.e. variation in expiratory airflow that is greater than that seen in healthy people (variable airflow limitation) – e.g. by spirometry in adults and in children old enough to perform the test – but it is not necessary to demonstrate airway hyperresponsiveness in a laboratory test or to demonstrate the presence of inflammatory cells in the airway. Respiratory symptoms may be due to many conditions other than asthma, so:

- the diagnosis of asthma is based on the probability that symptoms and clinical findings are due to asthma
- to confirm the diagnosis, lung function testing must be done at a time when the person does not have a respiratory tract infection[3]
- the evidence for variable airflow limitation must be documented at the time of diagnosis
- in young children, especially pre-schoolers (who cannot perform spirometry), it can be difficult to diagnose asthma with certainty.

## In this section

*Special terms*

Definitions of special terms used the handbook, including descriptions of inhaled corticosteroid dose levels and specific aspects of asthma

**http://www.asthmahandbook.org.au/resources/definitions/special-terms**

*Glossary*

Explanation of abbreviations used in the handbook, technical terms, and terms for which alternatives are commonly used

**http://www.asthmahandbook.org.au/resources/definitions/glossary**

## References

1. Global Initiative for Asthma (GINA). *Global strategy for asthma management and prevention*. GINA, 2012. Available from: http://www.ginasthma.org
2. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. *Lancet*. 2008; 372: 1107-19. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18805339

3. Melbye H, Kongerud J, Vorland L. Reversible airflow limitation in adults with respiratory infection. *Eur Respir J*. 1994; 7: 1239-1245. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7925901

# Definitions of special terms

### *Asthma*

A chronic lung disease, which can be controlled but not cured.

Untreated asthma is usually characterised by chronic inflammation involving many cells and cellular elements, which is associated with airway hyperresponsiveness and intermittent airway narrowing due to any (or a combination) of bronchoconstriction, congestion or oedema of bronchial mucosa, and mucus.

Asthma probably represents a spectrum of conditions with different pathophysiological mechanisms.

In clinical practice, asthma is defined by the presence of both excessive variation in lung function and variable respiratory symptoms, such as wheeze, shortness of breath, cough and chest tightness.

### *Complementary and alternative therapies*

The range of medical and healthcare practices and products that are not generally considered part of conventional medicine provided by doctors and allied health professionals in Australia. These include 'natural' products, 'mind-and-body' therapies, dietary supplements or restrictions, and physical therapies.

### *Control*

Asthma control refers to the overall degree to which the impact of asthma, and the risks due to the underlying disease and its treatment, have been reduced or managed for the person.

Assessment of asthma control involves (both of):

- assessment of recent asthma symptom control (e.g. good, partial or poor), based on frequency of daytime asthma symptoms, night-time symptoms or symptoms on waking, reliever use in response to symptoms, and on limitation of activity, usually over the past 4 weeks
- assessment of risk factors for future adverse events (e.g. flare-ups, life-threatening asthma, accelerated decline in lung function, or adverse effects of treatment).

### *Flare-up*

Worsening of asthma control (increase in asthma symptoms)

Mild flare-up: Worsening of asthma control that is only just outside the normal range of variation for the individual (documented when patient is well)

Moderate flare-up: Worsening asthma that is troublesome or distressing to the patient and requires a change in treatment, but is not life-threatening and does not require hospitalisation

Severe flare-up: Event that requires urgent action by the patient (or carers) and health professionals to prevent a serious outcome such as hospitalisation or death from asthma

### *High-dose inhaled corticosteroids*

See Inhaled corticosteroids doses (adults), Inhaled corticosteroid doses (children)

### *Inhaled corticosteroid doses (adults)*

Low dose: 100–200 microg beclometasone dipropionate per day or 200–400 microg budesonide per day or 80–160 microg ciclesonide per day or 100–200 microg fluticasone propionate per day

Medium dose: 250–400 microg beclometasone dipropionate per day or 500–800 microg budesonide per day or 240–320 microg ciclesonide per day or 100 microg of fluticasone furoate* per day or 250–500 microg fluticasone propionate per day

High dose: more than 400 microg beclometasone dipropionate per day or more than 800 microg budesonide per day or more than 320 microg ciclesonide per day or 200 microg of fluticasone furoate* per day or more than 500 microg fluticasone propionate per day

*Fluticasone furoate is available only in combination with vilanterol (a long-acting beta$_2$ agonist), and is not available as a low dose. It should only be prescribed as one inhalation once daily.

*Table. Definitions of ICS dose levels in adults*

| Inhaled corticosteroid | Daily dose (microg) |
|---|---|

| | Low | Medium | High |
|---|---|---|---|
| *Beclometasone dipropionate †* | 100–200 | 250–400 | >400 |
| *Budesonide* | 200–400 | 500–800 | >800 |
| *Ciclesonide* | 80–160 | 240–320 | >320 |
| *Fluticasone furoate** | — | 100 | 200 |
| *Fluticasone propionate* | 100–200 | 250–500 | >500 |

† 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*

Respiratory Expert Group, Therapeutic Guidelines Limited. *Therapeutic Guidelines: Respiratory, Version 4*. Therapeutic Guidelines Limited, Melbourne, 2009.

GlaxoSmithKline Australia Pty Ltd. Product Information: *Breo (fluticasone furoate; vilanterol) Ellipta*. Therapeutic Goods Administration, Canberra, 2014. Available from: https://www.ebs.tga.gov.au/

GlaxoSmithKline Australia Pty Ltd. Product Information: *Arnuity (fluticasone furoate) Ellipta*. Therapeutic Goods Administration, Canberra, 2016. Available from: https://www.ebs.tga.gov.au/

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### *Inhaled corticosteroid doses (children)*

Low dose: 100–200 microg beclometasone dipropionate per day or 200–400 microg budesonide per day or 80–160 microg ciclesonide per day or 100–200 microg fluticasone propionate per day

High dose: more than 200 microg beclometasone dipropionate per day or more than 400 microg budesonide per day or more than 160 microg ciclesonide per day or more than 200 microg fluticasone propionate per day

*Table. Definitions of ICS dose levels in children*

| Inhaled corticosteroid | Daily dose (microg) | |
|---|---|---|
| | Low | High |
| *Beclometasone dipropionate †* | 100–200 | >200 (maximum 400) |
| *Budesonide* | 200–400 | >400 (maximum 800) |
| *Ciclesonide ‡* | 80–160 | >160 (maximum 320) |
| *Fluticasone propionate* | 100–200 | >200 (maximum 500) |

† 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*

van Asperen PP, Mellis CM, Sly PD, Robertson C. *The role of corticosteroids in the management of childhood asthma.* The Thoracic Society of Australia and New Zealand, 2010. Available from: http://www.thoracic.org.au/clinical-documents/area?command=record&id=14

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### *Low-dose inhaled corticosteroids*

See Inhaled corticosteroids doses (adults), Inhaled corticosteroid doses (children)

### *Medium-dose inhaled corticosteroids*

See Inhaled corticosteroids doses (adults)

### *Variable airflow limitation*

Variation in airflow beyond the range seen in healthy populations, measured by any of the following methods:

- spirometry before 10–15 minutes after administration of bronchodilator in a single session
- spirometry on separate visits
- spirometry before and after exercise
- spirometry before and after a treatment trial with an inhaled corticosteroid
- peak expiratory flow measured twice daily
- airway hyperresponsiveness testing (exercise challenge test or bronchial provocation test).

Variable airflow limitation is defined by specific criteria for each method.

### *Written asthma action plan*

An individualised set of instructions for a person with asthma (or their carer) to follow as asthma symptoms change, and which is updated from time to time by their health professional.

Written asthma action plans include a list of the person's usual asthma and allergy medicines and instructions on what to do when the person experiences asthma symptoms (e.g. how to change medication, when and how to start a course of oral corticosteroids, when and how to get medical care, and what to do in an asthma emergency). A range of templates is available from National Asthma Council Australia's asthma action plan library.

▶ Go to: National Asthma Council Australia's *Asthma Action Plan Library*

# Abbreviations and explanations of terms

ACE inhibitors
: angiotensin converting enzyme inhibitors

aspirin-exacerbated respiratory disease
: also called aspirin/NSAID-intolerant asthma or aspirin-sensitive asthma

Asthma Score
: also called 'Asthma Control Test'

beclometasone
: or beclomethasone

Category A
: [Therapeutic Goods Administration pregnancy safety category A] drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

Category B1
: [Therapeutic Goods Administration pregnancy safety category B1] drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

Category B2
: [Therapeutic Goods Administration pregnancy safety category B2] drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

Category B3
: [Therapeutic Goods Administration pregnancy safety category B3] drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Category C
: [Therapeutic Goods Administration pregnancy safety category C] drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.

CFC
: chlorofluorocarbon

COPD
: chronic obstructive pulmonary disease

COX
: cyclo-oxygenase

DXA
: dual-energy X-ray absorptiometry

ED
: emergency department

EIB
: exercise-induced bronchoconstriction

Evidence-based recommendation (Grade A)
: Body of evidence can be trusted to guide practice

Evidence-based recommendation (Grade B)
: Body of evidence can be trusted to guide practice in most situations

Evidence-based recommendation (Grade C)
: Body of evidence provides some support for recommendation but care should be taken in its application

Evidence-based recommendation (Grade D)
: Body of evidence is weak and recommendation must be applied with caution

FEV
: forced expiratory volume over a specified time period:

  $FEV_1$: forced expiratory volume over one second
  $FEV_6$: forced expiratory volume over six seconds

flare-up
: exacerbation

flare-ups
: exacerbations

FSANZ
: Food Standards Australia and New Zealand

FVC
: forced vital capacity

GORD
: gastro-oesophageal reflux disease

HFA
: formulated with hydrofluoroalkane (CFC-free) propellant

ICS
: inhaled corticosteroid

ICU
: intensive care unit

IgE
: Immunoglobulin E

IL
: interleukin

IU
: international units

IV
: intravenous

LABA
: long-acting $beta_2$-adrenergic receptor agonist

LAMA
: long-acting muscarinic antagonist (long-acting anticholinergic bronchodilator)

LTRA
: leukotriene receptor antagonist

MBS
: Medical Benefits Scheme

NHMRC
: National Health and Medical Research Council

NIPPV
: non-invasive positive pressure ventilation

NSAIDs
: nonsteroidal anti-inflammatory drugs

occupational asthma
: new-onset asthma due to workplace factors

OCS
: oral corticosteroids

OSA
: Obstructive sleep apnoea

PaCO

carbon dioxide partial pressure on blood gas analysis

PaO
: oxygen partial pressure on blood gas analysis

PBS
: Pharmaceutical Benefits Scheme

PEF
: peak expiratory flow

pMDI
: pressurised metered-dose inhaler or 'puffer'

PPE
: personal protective equipment

preventer
: sometimes called controller

SABA
: short-acting beta$_2$-adrenergic receptor agonist

SAMA
: short-acting muscarinic antagonist (short-acting anticholinergic bronchodilator)

SaO2
: oxygen saturation

SpO2
: peripheral capillary oxygen saturation measured by pulse oximetry

TGA
: Therapeutic Goods Administration

upper airway dysfunction
: a spectrum of conditions characterised by inducible airway obstruction, including vocal cord dysfunction (also called paradoxical vocal cord movement)

work-exacerbated asthma
: worsening of asthma control due to workplace factors