Triple therapy for asthma in primary care

National Asthma Council | Australian Asthma Handbook

Triple therapy is a targeted treatment for severe asthma in some individuals, not a routine step-up from ICS-LABA treatment.

The National Asthma Council's Australian Asthma Handbook recommendations for managing difficult-to-treat asthma have changed.

If asthma is not adequately controlled by maintenance treatment with a medium* dose of inhaled corticosteroid (ICS) in combination with a long-acting beta$_2$ agonist (LABA):

1. Assess adherence, inhaler technique and other common causes before confirming severe asthma.
2. Complete initial investigations including spirometry, fractional exhaled nitric oxide (FeNO) test, and blood eosinophil count.
3. Offer specialist referral.
4. Consider a short treatment trial of add-on long-acting muscarinic antagonist (LAMA) or high-dose ICS-LABA.

What is triple therapy?

Triple therapy means maintenance treatment with an inhaled corticosteroid, a long-acting beta$_2$ agonist, and long-acting muscarinic antagonist.

Options include:

- tiotropium in a separate inhaler added to any ICS-LABA combination
- single-inhaler ICS-LABA-LAMA combinations.

When can triple therapy be considered for adults and adolescents?

Triple therapy is one of two options for those with severe asthma, pending specialist referral. It should also be considered for adults with longstanding asthma who have developed persistent expiratory airflow limitation‡ despite ICS-LABA treatment.

Initial investigation (Table 1) followed by referral is recommended when good asthma control cannot be achieved despite treatment with medium-dose ICS-LABA. If referral is not immediately available, consider a short treatment trial with either high-dose ICS-LABA or ICS-LABA-LAMA (medium–high ICS dose). If type 2 airway inflammation is identified (raised eosinophil count and/or raised FeNO) arrange immediate specialist assessment for monoclonal antibody therapy to reduce exacerbation risk (Figure 1).

When can ICS-LABA-LAMA treatment be considered for children?

Tiotropium is an add-on treatment for severe asthma (Table 2).

What are the clinical benefits of triple therapy?

In adults and adolescents with uncontrolled asthma, some but not all randomised controlled trials have reported reductions in severe exacerbations with triple therapy, compared with ICS-LABA alone.[1-3] Modest improvements in lung function have consistently been reported with triple therapies.[1,2,4,5] In children aged 6–11 years with symptomatic asthma, adding tiotropium to ICS-LABA reduces exacerbations and improves lung function and symptom control, compared with ICS-LABA alone.[6]

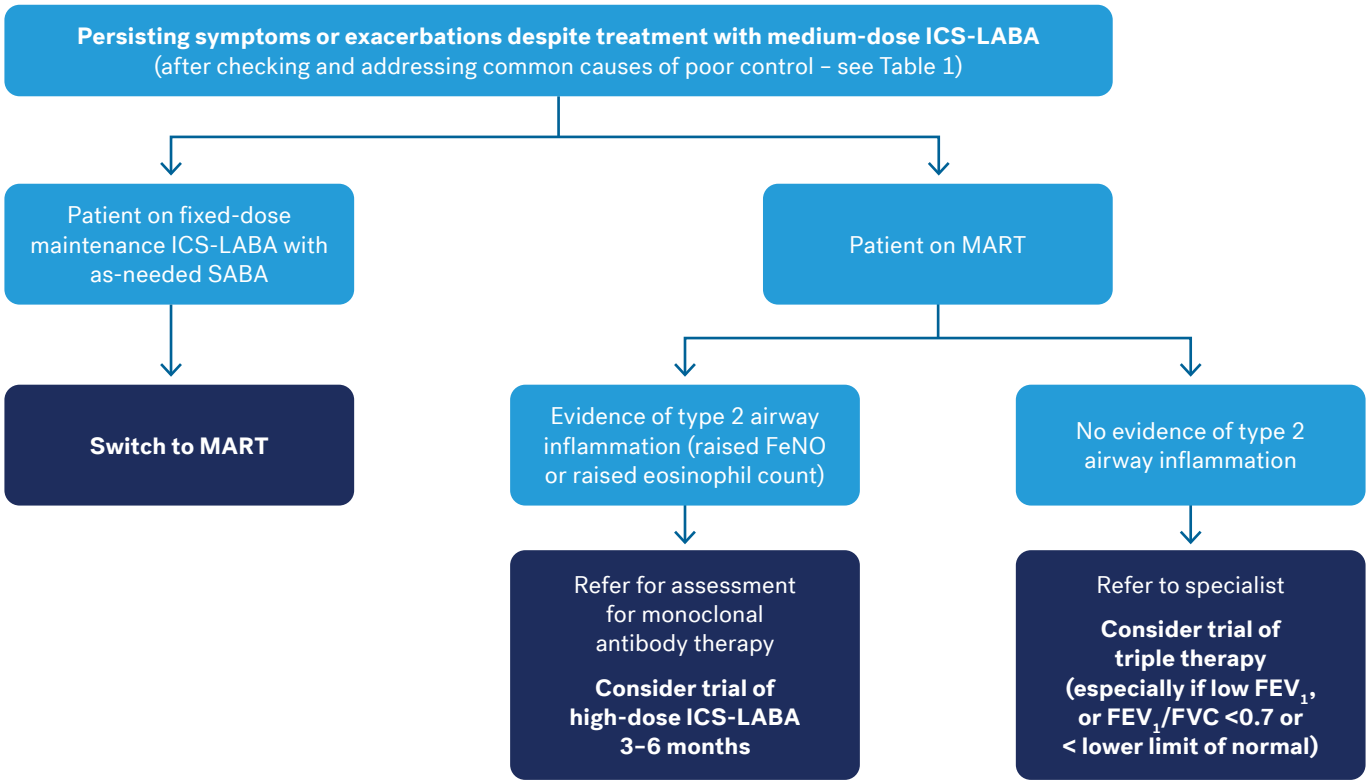
** Medium-dose ICS in patients aged 12+ years: total daily dose beclometasone 250–400 microg, budesonide 500–800 microg, fluticasone propionate 250–500 microg, or equivalent (see* Australian Asthma Handbook Medicines guide*).*

‡ Ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity < 0.07 (or below lower limit of normal), and FEV_1 <80% predicted value on pre-bronchodilator spirometry, regardless of bronchodilator responsive.

Table 1. Initial investigation of difficult-to-treat asthma in primary care

Assess adherence to ICS-containing treatment and address poor adherence.
Assess inhaler technique and correct if necessary.
Check for psychosocial factors affecting asthma self-management and address as necessary.
Refer to an accredited respiratory laboratory for spirometry and FeNO test. Consider alternative diagnoses if normal spirometry despite frequent symptoms. Persistent airflow limitation despite ICS-LABA treatment suggests potential benefit from adding LAMA. Raised FeNO despite medium–high ICS treatment indicates type 2 airway inflammation and potential indication for monoclonal antibody therapy.
Obtain blood eosinophil count to assess type 2 airway inflammation and potential indication for monoclonal antibody therapy.

Figure 1. Managing severe asthma in patients aged 12+ years



FeNO: fractional exhaled nitric oxide; MART: maintenance-and-reliever therapy

Table 2. LAMA (add-on) and triple therapies approved for asthma treatment

Active ingredients	Brand name (Inhaler type)	Age restriction (years)	Strength(s) (microg)	Dose	TGA-approved indication	PBS criteria* (severe asthma)
Tiotropium	***Spiriva Respimat*** (SMI)	≥ 6	2.5	2 inhalations once daily	Add-on maintenance treatment for moderate-to-severe asthma	**Adults:** ≥ 1 exacerbation requiring systemic corticosteroid in the 12 months before diagnosis of severe asthma despite optimised† asthma treatment and after checking adherence and inhaler technique. In combination with ICS and LABA (unless contraindicated). **Children:**‡ inadequate asthma control (including frequent moderate asthma exacerbations AND at least one severe exacerbation requiring systemic corticosteroid in previous 12 months) despite optimised§ asthma therapy with documented formal assessment of adherence, correct inhaler technique. In combination with medium-to high-dose ICS and LABA (unless LABA contraindicated).
Mometasone Indacaterol Glycopyrronium	***Enerzair Breezhaler*** (DPI)	≥ 18	68/114/46 136/114/46	2 inhalations per capsule daily	Maintenance treatment for asthma not adequately controlled by maintenance ICS-LABA (including ≥ 1 exacerbations in the previous year)	≥ 1 exacerbation requiring systemic corticosteroid in previous 12 months despite optimised† asthma treatment and after checking adherence and inhaler technique.
Fluticasone furoate Vilanterol Umeclidinium	***Trelegy Ellipta*** (DPI)	≥ 18	200/25/62.5 100/25/62.5#	1 inhalation daily	Maintenance treatment for asthma not adequately controlled by maintenance ICS-LABA	**200/25/62.5:** ≥ 1 exacerbation requiring systemic corticosteroid in previous 12 months despite optimised† asthma treatment and after checking adherence and inhaler technique.
Beclometasone Formoterol Glycopyrronium	***Trimbow*** (pMDI)	≥ 18	100/6/10 200/6/10	2 inhalations twice daily	Maintenance treatment for asthma not adequately controlled by maintenance ICS-LABA (including ≥ 1 exacerbations in the previous year)	≥ 1 exacerbation requiring systemic corticosteroid in previous 12 months despite optimised† asthma treatment and after checking adherence and inhaler technique.

DPI: dry powder inhaler; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$ agonist; LAMA: long-acting muscarinic antagonist; MDI: metered-dose inhaler; pMDI: pressurised metered-dose inhaler, SMI: soft mist inhaler; TGA: Therapeutic Goods Administration

** Summary only: consult full PBS listings before prescribing.*

† Including adherence to maintenance treatment with combination of ICS (≥800 microg budesonide per day or equivalent) and a LABA.

‡ Must be treated by (or in consultation with) a respiratory physician, paediatric respiratory physician, clinical immunologist, allergist, paediatrician or general physician experienced in the management of severe asthma.

§ Including maintenance treatment with medium-to-high-dose ICS and LABA with good adherence. Montelukast is an alternative if LABA contraindicated, not effective or not tolerated.

 # TGA approved for asthma, but not subsidised on PBS for asthma.

Practice points

Many patients with severe asthma (those with persistent type 2 airway inflammation evidenced by raised blood eosinophil count or FeNO) will benefit from monoclonal antibody therapy, so prolonged triple therapy should not replace prompt specialist assessment.

In adults with uncontrolled moderate or severe asthma on ICS-LABA, increasing the ICS dose is generally more effective in reducing exacerbations than switching to ICS-LABA-LAMA at the same ICS dose if there is type 2 airway inflammation.[5]

The addition of LAMA to ICS-LABA is more likely to benefit adults with persistent airflow limitation than those with normal lung function, independent of baseline blood eosinophil count.[5]

Tiotropium in a separate inhaler can be added to MART (the recommended regimen for moderate–severe asthma), but single-inhaler triple combinations cannot be used for MART and so require switching to standard maintenance treatment plus SABA as needed.

Patients with asthma should never use a LAMA without concomitant ICS treatment, due to increased risk of exacerbations.[7]

Only certain LAMA-containing inhalers and strengths are approved by Therapeutic Goods Administration for the treatment of asthma (Table 2). Before prescribing, consult product information for adverse effects, warnings and precautions. Pharmaceutical Benefits Scheme (PBS) restrictions apply.

Key messages for patients

Almost everyone with asthma should be able to achieve good control, with very few symptoms or attacks.

If someone with asthma keeps having symptoms or attacks despite daily treatment, doctors need to find out why. Tests may be needed to find the right inhaler and the right dose.

Common reasons for someone's asthma being uncontrolled despite treatment include not inhaling correctly, skipping doses, other medical conditions, breathing smoke, allergies, and life problems.

Some specialist-only treatments can make a big improvement in asthma symptoms and attacks.

REFERENCES: 1. Kerstjens HAM, et al. Lancet Respir Med 2020; 8: 1000-1012. **2.** Virchow JC, et al. Lancet 2019; 394: 1737-1749. **3.** Oba Y, et al. Cochrane Database Syst Rev 2022; 12: CD013799. **4.** Sobieraj DM, et al. JAMA 2018; 319: 1473-1484. **5.** Lee LA, et al. Lancet Respir Med 2021; 9: 69-84. **6.** Rodrigo GJ, et al. Pediatr Allergy Immunol. 2017; 28: 573-578. **7.** Baan EJ, et al. Pulm Pharmacol Ther 2021; 71: 102074.

For more information, refer to the National Asthma Council's Australian Asthma Handbook: asthmahandbook.org.au

Asthma and COPD medications chart: nationalasthma.org.au/living-with-asthma/resources/health-professionals/charts/asthma-copd-medications-chart

Developed by the National Asthma Council Australia in collaboration with

Clinical Associate Professor Debbie Rigby
Advanced practice pharmacist

Professor Christine McDonald
Respiratory physician

Dr Brett Montgomery
General practitioner

Professor Peter Wark
Respiratory physician

This information was developed independently by the National Asthma Council Australia with support from GlaxoSmithKline (GSK Australia).