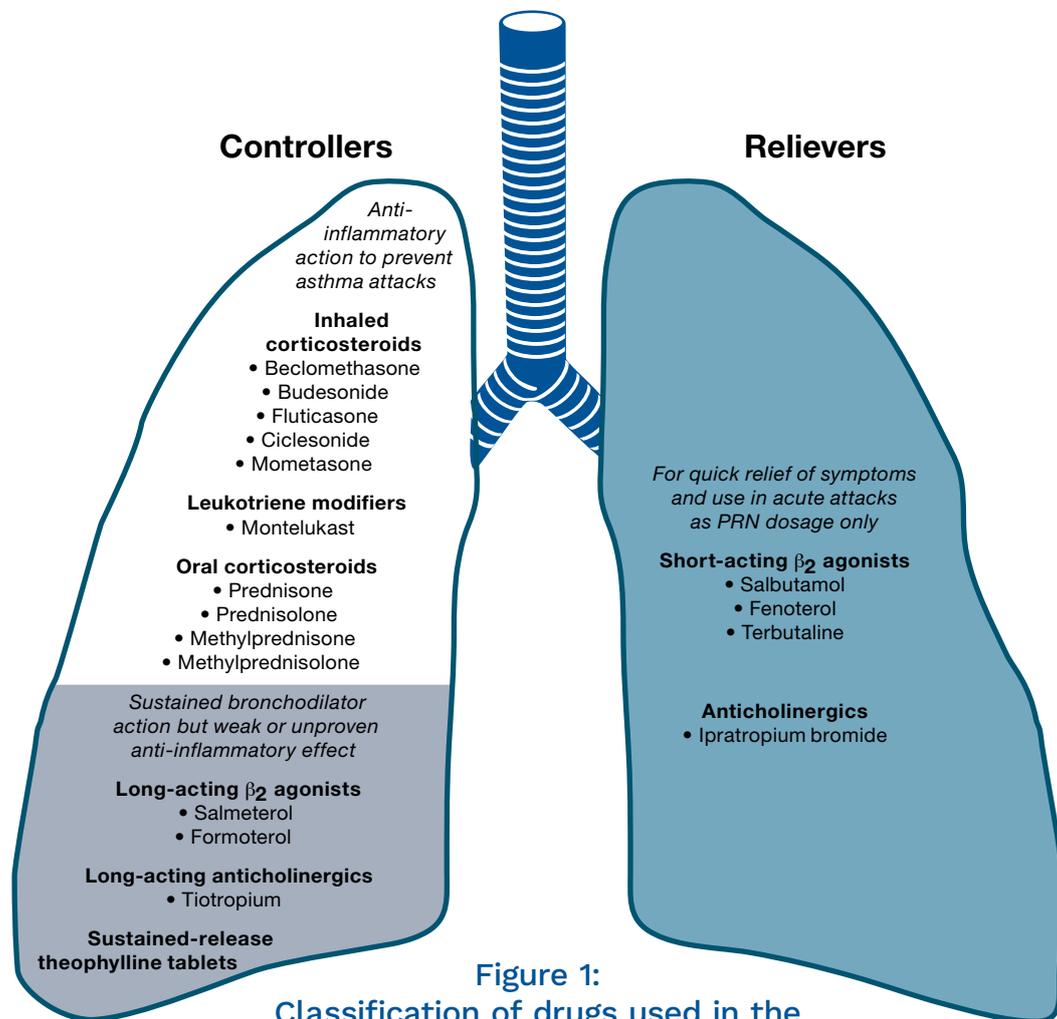




# The treatment of asthma

Asthma prevalence is increasing worldwide and surveys indicate that the majority of patients in developed and developing countries do not receive optimal care.



**Figure 1:**  
Classification of drugs used in the maintenance treatment of asthma



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The goal of asthma treatment is to achieve control of the disease for prolonged periods, taking into account the safety and cost of treatment required to achieve this. This article provides a brief overview of treatments available for asthma maintenance treatment, as well as newer therapeutic options.

## 1. Implementing treatment for chronic asthma

**Avoidance of triggers**, wherever possible, helps to minimise asthma severity and reduces asthma exacerbations. This includes avoidance of exposure to personal and second-hand tobacco smoke, reduction in exposure to furry animals, pollen, house dust mite and other allergens in those asthmatics known to be allergic, avoidance of sensitisers and irritants (dust and

fumes) which aggravate or cause asthma, and avoidance of drugs that may aggravate asthma such as  $\beta$  blockers, aspirin and nonsteroidal anti-inflammatory drugs.

**Pharmacotherapy** is the cornerstone of asthma management, with appropriate medications and delivery devices to meet patients' needs and circumstances.

When asthma is first diagnosed, it is convenient for implementation of treatment to classify it by SEVERITY as mild intermittent or chronic persistent asthma that is mild, moderate or severe.

After therapy is initiated, the emphasis for clinical management changes to the assessment of asthma CONTROL, which is the degree to which the manifestations of asthma are minimised by therapeutic intervention and the goals of therapy are met.



## 2. Routes of administration of asthma drugs

Asthma treatment can be administered in different ways - inhaled, orally or parenterally (by subcutaneous, intramuscular, or intravenous injection). The major advantage of inhaled therapy is that drugs are delivered directly into the airways, producing higher local concentrations with significantly less risk of systemic side effects. Inhaled medications for asthma are available as pressurised metered-dose inhalers (pMDIs), breath-actuated MDIs, dry powder inhalers (DPIs), soft mist inhalers, and nebulisers (rarely indicated for the treatment of chronic asthma). Choice of delivery device should be based on correct technique and patient preference, and be assessed during asthma reviews. Most patients make mistakes with a pMDI alone. They are less likely to do so if they also use a large volume (500 ml) spacer or holding chamber to improve drug delivery, increase lung deposition, and reduce local and systemic side effects.

## 3. Classification of asthma drugs

A classification of asthma drugs based on current knowledge of their mode of action is represented in Table 3. They may be:

- » **Relievers** - short-acting bronchodilators with rapid onset of action that provide acute relief of symptoms
- » **Controllers** - drugs with anti-inflammatory and/or a sustained bronchodilator action.

Treatment combinations are necessary in patients with more severe asthma or mild asthma not responsive to low dose inhaled corticosteroids.

### 3.1 Controllers

There are two groups of controllers - those with anti-inflammatory action

(corticosteroids and leukotriene blockers) and those with a sustained bronchodilator action (long-acting  $\beta_2$  agonists, long acting anti-cholinergics and slow-release theophyllines).

Anti-inflammatory treatment is recommended for all patients with chronic persistent asthma. Inhaled corticosteroids are the most widely studied and recommended drugs in this class. Leukotriene modifiers are effective, but less so than inhaled corticosteroids. Theophyllines have also been shown to have weak anti-inflammatory effects.

### 3.1.1 Corticosteroids

#### 3.1.1.1 Inhaled corticosteroids (ICS)

Inhaled corticosteroids are the mainstay of treatment for patients with chronic persistent asthma. The inhaled route is preferred because delivery directly to the lungs permits the use of lower doses.

Through their anti-inflammatory effects, inhaled corticosteroids reduce airway inflammation, decrease bronchial hyperresponsiveness and improve asthma control. In addition, they may modify airway remodelling and prevent an accelerated decline in lung function. Their long-term use in adequate doses has been shown to decrease exacerbations and mortality. There are several inhaled corticosteroids available and their equivalent doses in comparison with beclomethasone dipropionate (BDP) are shown in Table 1.

Systemic absorption of inhaled corticosteroids arises from oropharyngeal absorption and to a lesser extent from drug deposited in the lungs. This may be reduced by the use of a spacer device combined with mouth washing after inhalation. The former increases the fraction delivered to the lung. Both measures reduce the incidence of local side effects such as dysphonia and oropharyngeal candidiasis.

Inhaled corticosteroids are generally administered twice daily, but budesonide and ciclesonide are also approved for once daily use in milder asthma. A low starting dose is 200-500  $\mu\text{g}/\text{day}$  of BDP equivalent and a dose above 1000  $\mu\text{g}/\text{day}$  is considered a high dose. At higher doses, the dose-response curve is relatively flat but the risk of systemic side effects may be increased.

In older children and adults, a preferred strategy to reduce the dose of corticosteroids and improve control is the combination of long-acting  $\beta_2$  agonists (salmeterol or formoterol) with lower doses of inhaled corticosteroids. An alternative is the combination of lower dose inhaled corticosteroids with leukotriene blockers, which is a preferred combination in younger children. If these are unavailable, combination with slow-release theophyllines is a weaker alternative. Long-acting  $\beta_2$  agonists and slow-release theophylline must always be used in combination with at least low dose corticosteroids

Asthma treatment can be administered in different ways - inhaled, orally or parenterally.

**Table 1: Low, medium and high doses of inhaled corticosteroids: estimated clinical comparability**

Adults and adolescents $\geq 12$ years			
Drug	Daily dose (mcg)		
	Low	Medium	High
Beclomethasone dipropionate CFC	200-500	>500-1000	>1000
Beclomethasone dipropionate HFA	100-200	>200-400	>400
Budesonide (DPI or HFA)	200-400	>400-800	>800
Ciclesonide HFA	80-160	>160-320	>320
Fluticasone furoate (DPI)	100	n/a	200
Fluticasone propionate (DPI)	100-250	>250-500	>500
Fluticasone propionate (HFA)	100-250	>250-500	>500
Mometasone furoate	110-220	220-440	>440
Children 6-11 years			
Beclomethasone dipropionate CFC	100-200	>200-400	>400
Beclomethasone dipropionate HFA	50-100	>100-200	>200
Budesonide (DPI or HFA)	100-200	200-400	>400
Ciclesonide HFA	80	80-160	>160
Fluticasone furoate (DPI)	Not yet studied in this age group		
Fluticasone propionate (DPI)	100-200	>200-400	>400
Fluticasone propionate (HFA)	100-200	200-500	>500
Mometasone furoate	110	220-400	>440



for maintenance treatment of asthma.

The inhaled corticosteroid dose should be adjusted according to the level of control attained. Once control of asthma is achieved, the dose of medication should be carefully titrated to the minimum dose required to maintain control, thus reducing the potential for adverse effects.

Nebulised corticosteroids are expensive, require high-pressure nebulisers for optimal delivery, and are not recommended for routine use in chronic asthma.

### Side effects

Most studies evaluating the systemic effects of ICS suggest that clinically effective doses of ICS are safe and the potential risks are well balanced by the clinical benefits. However, studies using higher doses have been associated with detectable systemic effects on both growth and the hypothalamo-pituitary (HPA) axis. Although there are fewer studies in children younger than five years, the available data are similar to those from older children. Generally, low doses of ICS have not been associated with any clinically important adverse systemic effects in clinical trials, and long-term use is considered safe. Local side effects, such as hoarseness and candidiasis,

can occur, but are rare when a spacer is used.

### Efficacy in children

Most children are controlled on low daily doses of ICS (100-200 µg budesonide or equivalent). Some children require higher doses (400 µg/day) for control and for protection against exercise-induced symptoms. Clinical improvement occurs rapidly within 1-2 weeks, although maximum improvement may occur only after many weeks. Symptoms may recur after stopping ICS, with control deteriorating within weeks.

Several studies of ICS in young children under the age of five years with asthma have shown similar clinical effects to those in older children, including increases in lung function and number of symptom-free days, and a reduction in symptoms, need for additional medication, caregiver burden, systemic glucocorticosteroid use, and exacerbations. In young children, use of ICSs for up to two years has not been shown to induce remission of asthma; symptoms usually return when treatment is stopped.

#### 3.1.1.2 Oral corticosteroids

Oral corticosteroids are widely used for acute exacerbations of asthma at doses of 1-2 mg/kg/day for 3-7 days. Longer-term

oral corticosteroids may be considered in patients with poorly controlled asthma on high doses of inhaled corticosteroids and additional controller medications. Long-term oral corticosteroids (> 7.5 mg prednisone/day), while relatively inexpensive, are associated with serious systemic side effects, including growth suppression, obesity and adrenal suppression. Patients for whom long-term corticosteroids are being considered should be referred to a specialist for review. Alternate day dosing may reduce side effects. In patients on oral steroids, increased dosage should be given during episodes of increased stress, e.g. surgery.

#### 3.1.2 Leukotriene modifiers

Leukotriene modifiers (e.g. montelukast) are orally administered and act to antagonise the leukotriene receptor and thus resulting in an anti-inflammatory action via a different pathway to corticosteroids. They have a rapid onset of action (1-3 hours) and have been shown to exert their effect within days of commencing treatment. They may be used in patients with at least mild persistent asthma as add-on treatment to inhaled corticosteroids and may be of value in patients with aspirin-sensitive asthma and exercise induced asthma in combination with inhaled corticosteroids. As



add-on treatment in children whose asthma is insufficiently controlled by low doses of inhaled glucocorticosteroids, leukotriene modifiers provide moderate clinical improvements, including a significant reduction in exacerbations.

Not all patients respond, so if no benefit is evident after four weeks, the leukotriene modifiers should be withdrawn.

Leukotriene receptor antagonists are safe and effective for treatment of asthma in young children, from as early as six months of age. In pre-school children, LTRAs have been proposed as alternative first-line therapy to ICSs for episodic or mild persistent asthma, particularly in children who have difficulty in utilising inhalation treatment, with poor compliance, or with exercise-induced bronchospasm (EIB). Their routine use as monotherapy in asthma in adults is not advised.

Another potential role for leukotriene modifiers is in those patients with co-morbid asthma and allergic rhinitis, as their anti-inflammatory action extends from the nasal mucosa to the bronchial tree. This is in line with the concept of the 'united air way' disease in which asthma and allergic rhinitis are regarded as manifestations of a single disorder, and treating one disease may affect the control of the other.

### Side effects

Leukotriene modifiers are generally very well tolerated. Headaches and gastrointestinal upset are the most commonly encountered side effects. Skin rashes or flu like symptoms are much less common. Post marketing surveillance has shown agitation, irritability, anxiousness, insomnia and nightmares in a small proportion of patients.

### 3.1.3 Long-acting $\beta_2$ agonists (LABAs)

Salmeterol and formoterol are LABAs currently available in

SA and are administered twice daily. LABAs can be added to low to medium doses of inhaled corticosteroids instead of increasing the dose of inhaled corticosteroid further. They are useful for control of nocturnal symptoms and exercise-induced asthma. Studies have reported improvements in peak flow and lung function with the addition of a LABA. However, the effect on symptoms, need for rescue medication and frequency of exacerbations has been less consistent. LABAs as monotherapy have been associated with an increase in asthma-related mortality so they must always be taken together with an inhaled corticosteroid. Combination products (i.e. those containing an inhaled corticosteroid and a LABA in the same device) are preferable to administration via separate inhalers.

Fixed combination inhalers ensure that the LABA is always accompanied by an ICS. Combination products available in South Africa are *fluticasone/salmeterol* and *budesonide/formoterol*. Newer inhaled steroid/LABA combinations include fluticasone furoate/vilanterol and mometasone furoate/formoterol will soon be available in SA.

LABAs have been inadequately studied in children under four years of age, so are currently not recommended in this age group. Some patients may not respond to LABAs. LABAs are generally well tolerated. Side effects are similar in type and frequency to those of short-acting bronchodilators (SABAs), and include muscle tremor, headache and palpitations.

Both salmeterol and formoterol have sustained bronchodilator activity, but differ in the time of onset of action. The time of onset of salmeterol is delayed but formoterol has a rapid onset of bronchodilation (within 10-15 minutes of administration)

similar to that of short-acting B2 agonists. In addition, formoterol has a wider dose range, whereas salmeterol has an upper dose limit of 50ug bd. Formoterol / ICS combinations are thus suitable to be used for both control and relief of asthma symptoms.

### 3.1.4 Slow-release (SR) Theophyllines

Theophylline can be used in the treatment of asthma mainly as a bronchodilator (10-20 mg/kg/day), though it may also have anti-inflammatory effects at lower doses (5-10 mg/kg/day).

The anti-inflammatory effects of theophylline are small (less than that of low-dose ICSs) and side effects are common.

Theophylline may be used as alternative, adjunctive therapy with ICSs in children older than five years old and in adults. They should not be used as monotherapy.

Most formulations of SR theophyllines have a 12 hour and some a 24 hour duration of action. They are administered orally. There is no role for oral short-acting theophyllines in chronic asthma.

Their disadvantages include a narrow therapeutic range, drug interactions and frequent side effects (nausea, vomiting, abdominal pain, gastro-oesophageal reflux, palpitations, insomnia, irritability and seizures). More serious side effects such as arrhythmias and gastric bleeding may occur. These side effects are mainly seen at doses > 10 mg/kg/day. The risk of adverse effects is reduced if treatment is initiated with daily doses around 5 mg/kg/day and then gradually increased to 10 mg/kg/day. Severe overdosing with theophylline can be fatal.

Monitoring of serum theophylline concentration is essential. Long-term treatment with theophylline is not generally recommended in young children because of its adverse effects.

**1-2**  
**weeks:**  
clinical  
improvement  
happens rapidly



Consider stepping down when asthma symptoms have been well controlled and lung function has been stable

### 3.1.5 Other long term treatment options Immunotherapy

Allergen immunotherapy should be considered for patients who have persistent asthma if there is clear evidence of a relationship between symptoms and exposure to an allergen to which the patient is sensitive.

Both subcutaneous and sublingual immunotherapy has an effect on inflammatory parameters and bronchial hyperreactivity in asthmatics sensitised to house dust mites. Sublingual immunotherapy is the safer option and could be used as adjunctive treatment to pharmacotherapy in adults and children older than five years old with rhinitis and mild to moderate asthma (FEV<sub>1</sub> >80%), to enhance asthma control.

*Immunosuppressives* including methotrexate may rarely be of benefit in refractory asthmatics. Patients considered for this treatment must be referred to a specialist.

*Antihistamines* are ineffective in the treatment and prevention of asthma.

### Dietary changes

There is little scientific evidence that exclusion diets are useful in the treatment of asthma. As such, they are not routinely recommended.

Several cross-sectional studies have shown that low serum levels of *Vitamin D* are linked to impaired lung function, higher exacerbation frequency and reduced corticosteroid response. However, to date, Vitamin D supplementation has not been associated with improvement in asthma control or reduction in exacerbations.

## 4. "Newer" treatment modalities for asthma

### 4.1 Long Acting Anti-Cholinergics

Tiotropium bromide is an inhaled, once daily anticholinergic bronchodilator which binds to all three

muscarinic receptors to produce a long acting bronchodilator effect and possibly an anti-inflammatory effect. It was initially approved for COPD, but recently (2015) added on as a late step in adult chronic asthma guidelines as a treatment option in patients with uncontrolled asthma despite high doses of inhaled corticosteroids and LABAs. Tiotropium is available as a dry powder inhaler or pMDI, and is licensed for adults and adolescents over the age of 12 years in a once daily dose. Studies have shown an improvement in lung functions and a reduction in exacerbations in patients with uncontrolled asthma.

## 4.2 Monoclonal antibodies

### 4.2.1 Omalizumab (anti IgE)

Omalizumab is a recombinant humanised monoclonal anti-IgE antibody. It binds free IgE in blood and interstitial fluid and to the membrane-bound form of IgE on the surface of mIgE-expressing B-lymphocytes. It is licensed as an add-on treatment in severe persistent asthma in adults, adolescents and children over the age of six years with evidence of allergic sensitisation and IgE levels of up to 1500 kU/L. There is also some evidence for its efficacy at higher IgE levels. Studies have shown improvement in quality of life as well as reductions in severe exacerbations in patients on omalizumab. Omalizumab is given subcutaneously every 2-4 weeks and courses of at least six months are recommended for severe asthma in suitable patients.

### 4.2.2 Mepolizumab (anti interleukin-5)

Mepolizumab is a fully humanised anti-interleukin 5 (IL-5) monoclonal IgG1 antibody that binds to free IL5 and prevents its association with the IL5 receptor on eosinophils. In clinical trials it has been shown to reduce airways

and blood eosinophils and reduce asthma exacerbations. Mepolizumab has recently been added on to the step-up guidelines for severe asthma uncontrolled on high dose inhaled steroids and LABAs. It should be given in specialist referral centres only and is licensed for over the age of 12 years.

### 4.2.3 Dupilumab (anti interleukin 4)

Dupilumab is a fully human monoclonal antibody directed against the body's interleukin (IL)-4 receptors, intended to inhibit the downstream effects of type 2 mucosal immunity cytokines, IL-4 and IL-13. Both are cytokines believed to play a major role in the manifestation of allergic diseases. Studies have shown dupilumab to be efficacious as an add-on therapy to medium-to-high-dose inhaled corticosteroids plus a long-acting  $\beta_2$  agonist in patients with uncontrolled persistent asthma. Improvement has been demonstrated in baseline forced expiratory volume in 1 s (FEV<sub>1</sub>), as well as a reduction in annualised exacerbation rates and improvements in quality of life and asthma control. Efficacy was more evident when injections were given every two weeks compared with every four weeks.

Treatment algorithms for the management of chronic asthma in accordance with GINA (Global Initiative for Asthma) guidelines 2016 are advised.

## 5. Stepping down asthma treatment

Consider stepping down when asthma symptoms have been well controlled and lung function has been stable for three or more months. This should be done under close supervision. Asthma is considered well controlled if:

- »  $\leq 2$  daytime symptoms/week
- » No limitation of activities
- » No nocturnal symptoms/awakenings



- » Reliever medication < twice/ week
- » Normal lung function
- » No exacerbations.

## 6. Conclusion

Initial assessment of asthma severity and ongoing assessment of asthma control provide guides to asthma therapy, which should be based on GINA guidelines. Medications and delivery devices should be appropriate to meet patients' needs and circumstances. Anti-inflammatory treatment is recommended for all patients with chronic persistent asthma. Inhaled corticosteroids are still the most widely studied and recommended drugs in this class.

Leukotriene modifiers and theophyllines are effective oral forms of treatment, usually combined with inhaled corticosteroids. Long acting beta agonists and anti-cholinergics provide sustained bronchodilation, only to be used in conjunction with inhaled corticosteroids. Several antibodies such as anti-IgE, anti-IL5 and anti-IL4 have recently been used in asthma therapy in selected patients with more severe asthma.

## References and Recommended Reading

1. GINA Report 2016. Global Strategy on Asthma Management and Prevention. [www.ginasthma.org](http://www.ginasthma.org) accessed December 2016
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3. South African Childhood Asthma Working Group: Motala C, Green R, Manjra A, Zar H, Kling S et al. Guideline for the management of chronic asthma in children- 2009 update. ALLSA Handbook 2010
4. Caminati M, Duric-Filipovic I, Arasi S, Peroni DG, Zivkovic Z, Senna G. Respiratory allergies in childhood: recent advances and future challenges. PAI 2015;26:702. **SF**

# Multiple choice questions

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**1** Surveys indicate that the majority of patients in developed and developing countries do not receive optimal care.

- a. True
- b. False

**A**  
**B**

**2** Avoidance of triggers, wherever possible, helps to minimise asthma severity and reduces asthma exacerbations. This include:

- a. Tobacco smoke, pollution and dirt
- b. Tobacco smoke, dust mites and sunlight
- c. Dust mites, grass and sunlight
- d. Tobacco smoke, pollen and dust mites

**A**

**B**

**C**

**D**

**3** Asthma treatment can be administered in different ways - inhaled, orally, or

- a. Parentally
- b. DTI
- c. Exhaled
- d. DPI

**A**

**B**

**C**

**D**

**4** Inhaled medications for asthma are available as pressurised metered-dose inhalers (pMDIs),

breath-actuated MDIs, dry powder inhalers (DPIs), soft mist inhalers, and nebulisers.

- a. True
- b. False

**A**  
**B**

**5** Controllers are - short-acting bronchodilators with rapid onset of action that provide acute relief of symptoms

- a. True
- b. False

**A**  
**B**

**6** There are two groups of controllers - those with \_\_\_\_\_ (corticosteroids and leukotriene blockers) and those with a

\_\_\_\_\_ (e.g. Long-acting  $\beta$ 2 agonists).

- a. Anti-inflammatory action and sustained anti-bronchodilator action
- b. Inflammatory action and sustained bronchodilator action
- c. Inflammatory action and sustained anti-bronchodilator action
- d. Anti-inflammatory action and sustained bronchodilator action

**A**

**B**

**C**

**D**

**7** A low starting dose is \_\_\_\_\_  $\mu$ g/day of BDP equivalent and a dose above \_\_\_\_\_  $\mu$ g/day is considered a high dose.

- a. 200-250 and 1000
- b. 250-500 and 750
- c. 200-500 and 1000
- d. 250-500 and 750

**A**  
**B**  
**C**  
**D**

**8** Leukotriene modifiers (e.g. montelukast) are parenterally administered and act to antagonise the leukotriene receptor and thus resulting in an anti-inflammatory action via a different pathway to corticosteroids.

- a. True
- b. False

**A**  
**B**

**9** Theophylline can be used in the treatment of asthma mainly as a bronchodilator

- a. True
- b. False

**A**  
**B**

**10** Dupilumab is a fully human monoclonal antibody directed against the following interleukin receptor:

- a. (IL)-4
- b. (IL)-3
- c. (IL)-2
- d. (IL)-7

**A**  
**B**  
**C**  
**D**

**This is to state that I have participated in the CPD-approved programme and that these are my own answers.**

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