Drugs acting on the respiratory tract
**Antiasthmatic drugs**

**Asthma**

Asthma is a chronic inflammatory disease characterized by episodes of reversible airways obstruction due to bronchial hyperresponsiveness; inflammation may lead to irreversible obstruction in a few patients. A classification based on severity before the start of treatment and disease progression is of importance when decisions have to be made about management. It can be divided by severity into intermittent, mild persistent, moderate persistent and severe persistent. These are useful in the management of the disease since therapy has a stepwise approach which must be discussed with the patient before commencing therapy. The level of therapy is increased as the severity of the asthma increases with stepping-down if control is sustained (see tables on treatment below).

**INHALATION**

Medications for asthma can be administered in several different ways, including inhaled, oral and parenteral (subcutaneous, intramuscular, or intravenous). The main advantage of delivering drugs directly into the airways via inhalation is that high concentrations can be delivered more effectively and rapidly to the airways, and systemic adverse effects avoided or minimized.

It is important that patients receive careful instruction in the use of pressurized (aerosol) inhalation (using a metered-dose inhaler) to obtain optimum results. Before use, the inhaler should be shaken well. After exhaling as completely as possible, the mouthpiece of the inhaler should be placed well into the mouth and the lips firmly closed around it. The patient should inhale deeply through the mouth while actuating the inhaler. After holding the breath for 10 seconds or as long as is comfortable, the mouthpiece should be removed and the patient should exhale slowly.

It is important to check that patients continue to use their inhalers correctly as inadequate technique may be mistaken for drug failure. Spacing devices provide a space between the inhaler and the mouth. They may be of benefit for patients such as the elderly, small children and the asthmatic who find inhalers difficult to use or for those who have difficulty synchronizing their breathing with administration of the aerosol. A large volume spacing device is also recommended for inhalation of high doses of corticosteroids to reduce oropharyngeal deposition which can cause candidosis. The use of metered-dose inhalers with spacers is less expensive and may be as effective as use of nebulizers, although drug delivery may be affected by choice of spacing device.

Breath-actuated devices including dry powder inhalers are also available.

*Solutions for nebulization* are available for use in acute severe asthma. They are administered over a period of 5–10 minutes from a nebulizer, usually driven by oxygen in hospital.

**ORAL**
The oral route is used when administration by inhalation is not possible. Systemic adverse effects occur more frequently when a drug is given orally rather than by inhalation. Drugs given by mouth for the treatment of asthma include beta₂-agonists, corticosteroids, and theophylline.

**PARENTERAL**

Drugs such as beta₂-agonists, corticosteroids, and aminophylline may be given by injection in acute severe asthma when administration by nebulization is inadequate or inappropriate. If the patient is being treated in the community, urgent transfer to hospital should be arranged.

**PREGNANCY**

Poorly controlled asthma in pregnant women can have an adverse effect on the fetus, resulting in perinatal mortality, increased prematurity and low birth-weight. For this reason using medications to obtain optimal control of asthma is justified. Administration of drugs by inhalation during pregnancy has the advantage that plasma drug concentrations are not likely to be high enough to have an effect on the fetus. Acute exacerbations should be treated aggressively in order to avoid fetal hypoxia.

**Acute exacerbation of asthma**

Severe asthma can be fatal and must be treated promptly and energetically. Acute severe asthma attacks require hospital admission where resuscitation facilities are immediately available.

Severe asthma is characterized by persistent dyspnoea poorly relieved by bronchodilators, exhaustion, a high pulse rate (usually more than 110/minute) and a very low peak expiratory flow.

As asthma becomes more severe, wheezing may be absent. Patients should be given oxygen 40–60% (if available) (see also section 1.1.3). Patients should also be given salbutamol or terbutaline via a nebulizer. In emergencies where a nebulizer is not available, salbutamol 100 micrograms by aerosol inhalation can be repeated 10–20 times preferably using a large-volume spacing device. Patients should also be given a corticosteroid; for adults, prednisolone 30–60 mg by mouth or hydrocortisone 200 mg (preferably as sodium succinate) intravenously; for children, prednisolone 1–2 mg/kg by mouth (1–4 years, maximum 20 mg, 5–15 years, maximum 40 mg) or hydrocortisone 100 mg (preferably as sodium succinate) intravenously; if the patient experiences vomiting the parenteral route may be preferred for the first dose.

If response is inadequate, ipratropium by nebulizer should be considered. Most patients do not benefit from the addition of intravenous aminophylline or a parenteral beta₂-agonist; both cause more adverse effects than nebulized beta₂-agonists. Nevertheless, an occasional patient who has not been taking theophylline, may benefit from a slow intravenous infusion of aminophylline.

The use of epinephrine (adrenaline) (see section 3.1) in asthma has generally been superseded by beta₂-selective adrenoceptor agonists.
Treatment should **never** be delayed for investigations, patients should **never** be sedated and the possibility of pneumothorax should be considered. Patients who deteriorate further despite treatment may need intermittent positive pressure ventilation.

### TREATMENT OF CHRONIC ASTHMA:
#### INFANTS AND YOUNG CHILDREN UNDER 5 YEARS OLD

Preferred treatments are in bold print.

<table>
<thead>
<tr>
<th>Step</th>
<th>Severe Persistent</th>
<th>Long-term Preventive</th>
<th>Quick Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP 4</strong></td>
<td>Daily medications</td>
<td><strong>Inhaled corticosteroid</strong>, beclometasone dipropionate MDI with spacer and face mask &gt; 1 mg daily or nebulized beclometasone &gt; 1 mg twice daily</td>
<td><em>Inhaled short-acting bronchodilator: inhaled beta2-agonist</em> or ipratropium bromide as needed for symptoms, not to exceed 3–4 times daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step</th>
<th>Moderate Persistent</th>
<th>Daily medications</th>
<th><em>Inhaled short-acting bronchodilator: inhaled beta2-agonist</em> or ipratropium bromide as needed for symptoms, not to exceed 3–4 times daily</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP 3</strong></td>
<td><strong>Inhaled corticosteroid</strong>, beclometasone dipropionate MDI with spacer and face mask 400–800 micrograms daily or nebulized beclometasone 1 mg twice daily</td>
<td>Consider short course of soluble prednisolone tablets, regular inhaled long-acting beta2-agonist or modified-release theophylline Also, nebulized beta2-agonist</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step</th>
<th>Mild Persistent</th>
<th>Daily medications</th>
<th><em>Inhaled short-acting bronchodilator: inhaled beta2-agonist</em> or ipratropium bromide as needed for symptoms, not to exceed 3–4 times daily</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP 2</strong></td>
<td><strong>Either inhaled corticosteroid</strong>, beclometasone dipropionate, 400–800 micrograms, or cromoglicate (use MDI with a spacer and face mask or use a nebulizer)</td>
<td><em>Inhaled short-acting bronchodilator: inhaled beta2-agonist</em> or ipratropium bromide as needed for symptoms, not to exceed 3–4 times daily</td>
<td></td>
</tr>
</tbody>
</table>

| Step   | Intermittent | None needed | *Inhaled short-acting bronchodilator: inhaled beta2-agonist* or ipratropium bromide as needed for symptoms, but not more than once daily | *Intensity of treatment will depend on severity of attack Step up If control is not achieved, consider step up. But first: review patient medication |

---

**Step down**
Review treatment every 3 to 6 months. If control is sustained for at least 3 months, a gradual stepwise reduction in treatment may be possible.
### TREATMENT OF CHRONIC ASTHMA: ADULTS AND CHILDREN OVER 5 YEARS OLD

Preferred treatments are in bold print.

<table>
<thead>
<tr>
<th>STEP</th>
<th>Severe Persistent</th>
<th>Long-term Preventive</th>
<th>Quick Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Daily medications: • <strong>Inhaled corticosteroid</strong>, beclometasone dipropionate 0.8–2 mg + • Long-acting bronchodilator: <em>either long-acting inhaled beta2-agonist</em>, and/or modified-release theophylline, and/or long-acting beta2-agonist tablets or syrup + • corticosteroid tablets or syrup long term</td>
<td>• Short-acting bronchodilator: <strong>inhaled beta2-agonist</strong> as needed for symptoms</td>
</tr>
<tr>
<td>STEP 3</td>
<td>Moderate Persistent</td>
<td>Daily medications: • <strong>Inhaled corticosteroid</strong>, beclometasone dipropionate 0.8–2 mg daily in divided doses + if needed • Long-acting bronchodilator: <em>either long-acting inhaled beta2-agonist</em>, modified-release theophylline, or long-acting beta2-agonist tablets or syrup</td>
<td>• Short-acting bronchodilator: <strong>inhaled beta2-agonist</strong> as needed for symptoms, not to exceed 3–4 times daily</td>
</tr>
<tr>
<td>STEP 2</td>
<td>Mild Persistent</td>
<td>Daily medications: • Either <strong>inhaled corticosteroid</strong>, beclometasone dipropionate 100–400 micrograms twice daily, sodium cromoglicate or modified-release theophylline</td>
<td>• Short-acting bronchodilator: <strong>inhaled beta2-agonist</strong> as needed for symptoms, not to exceed 3–4 times daily</td>
</tr>
<tr>
<td>STEP 1</td>
<td>Intermittent</td>
<td>• None needed</td>
<td>• Short-acting bronchodilator: <strong>inhaled beta2-agonist</strong> as needed for symptoms (up to once daily) • Intensity of treatment will depend on severity of attack • Inhaled beta2-agonist or sodium cromoglicate before exercise or exposure to allergen</td>
</tr>
</tbody>
</table>

Step down
Review treatment every 3 to 6 months. If control is sustained for at least 3 months, a gradual stepwise reduction in treatment may be possible.

Step up
If control is not achieved, consider step up. But first: review patient medication technique, compliance and environmental control.

### Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (chronic bronchitis and emphysema) may be helped by an inhaled short-acting **beta2-adrenoceptor agonist** used as required or
when the airways obstruction is more severe, by an inhaled **anticholinergic**
(antimuscarinic) **bronchodilator** or both if necessary. Although many patients
are treated with an inhaled corticosteroid its role in chronic obstructive pulmonary
disease is not clear at present. A limited trial of high-dose inhaled corticosteroid or an oral
corticosteroid is recommended for patients with moderate airflow obstruction to
determine the extent of the airway reversibility and to ensure that asthma has not been
overlooked.

Long-term oxygen therapy prolongs survival in some patients with chronic
obstructive pulmonary disease.

**Beta2-adrenoceptor agonists (beta2-adrenoceptor stimulants)**

The adrenoreceptors in bronchi are mainly beta2 type and their stimulation causes
bronchial muscles to relax. The beta2-adrenoceptor agonists include salbutamol,
terbutaline, and fenoterol.

When salbutamol is given by inhalation (100–200 micrograms) the effect can last as
long as 4 hours thus making it suitable for both the treatment (see Tables) and
prevention of asthma. Salbutamol can also be taken orally in a dose of 2–4 mg up to 4
times daily but is less effective and causes more adverse effects. It can also be given
by injection for severe bronchospasm.

**ADVERSE EFFECTS**

Cardiovascular adverse effects (arrhythmias, palpitations and tachycardia) may occur
with salbutamol, but are infrequent with inhaled preparations. Hypokalaemia may
result from beta2-adrenoceptor agonist therapy. Particular caution is required in
severe asthma because this effect may be potentiated by concomitant treatment with
xanthines (for example theophylline), corticosteroids, diuretics and hypoxia. Plasma
potassium concentrations should be monitored in severe asthma.

**Xanthines**

Xanthines include theophylline and aminophylline. They relax bronchial smooth
muscle relieving bronchospasm and also stimulate respiration. Absorption of
theophylline from the gastrointestinal tract is usually rapid and complete. It is
metabolized by the liver but its half-life can vary considerably in certain diseases
including hepatic impairment and cardiac failure, with some coadministered drugs
(see Appendix 1) as well as by factors such as age, smoking and alcohol intake. The
half-life variation can be important because theophylline has a narrow margin
between therapeutic and toxic effects. At therapeutic doses some patients experience
nausea and diarrhoea and when plasma concentrations exceed the recommended range
of 10–20 mg/litre (55–110 micromol/litre) arrhythmias and convulsions which may be
fatal can occur. Monitoring of plasma concentrations is therefore recommended.
Theophylline is used to treat chronic asthma, usually in the form of modified-release
preparations which produce adequate plasma concentrations for up to 12 hours. It is
used as an adjunct to beta2-agonist or corticosteroid therapy when additional
bronchodilation is required but there is an increased risk of adverse effects with beta2-
agonists (see above). When given as a single dose at night, modified-release
preparations may be useful in controlling nocturnal asthma and early morning wheezing.

The absorption characteristics of modified-release theophylline preparations vary considerably and therefore it is important to keep the patient on the same brand-name formulation.

Theophylline is given by injection as aminophylline (a mixture of theophylline with ethylenediamine) which is 20 times more soluble in water than theophylline alone. It is administered by slow intravenous injection in severe asthma attacks.

**Corticosteroids**

**INHALED CORTICOSTEROIDS**

Inhaled corticosteroids, such as beclometasone, are the most effective anti-inflammatory medications for the treatment of asthma. They are recommended for the long-term control of asthma in patients using a beta\textsubscript{2} -adrenoceptor agonist more than once a day. Regular use of inhaled corticosteroids reduces the risk of exacerbations of asthma.

Corticosteroids must be used regularly to obtain maximum benefit. Symptom control is usually effective after 3 to 7 days treatment. Long-term high-dose regimens of inhaled corticosteroids are useful for the treatment of severe persistent asthma because they both reduce the need for the long-term use of oral corticosteroids and have fewer systemic adverse effects.

Local adverse effects from inhaled corticosteroids include oropharyngeal candidosis, dysphonia and occasional coughing from upper airway irritation. The use of spacing devices reduces oropharyngeal deposition and thus reduces the incidence of candidosis. The risk for systemic effects of inhaled corticosteroids is small and is dependent upon the dose and potency of the corticosteroid as well as its bioavailability and the plasma half-life of its systemically absorbed fraction. Systemic effects are rare and include skin thinning and easy bruising, a small increased risk of glaucoma and cataracts, adrenal suppression, decrease of bone metabolism and growth retardation in children.

**SYSTEMIC CORTICOSTEROIDS**

Oral corticosteroids (sections 3.1 and 18.1) may be used as ‘maximum therapy’ to achieve control of a patient’s asthma. This may be useful either when initiating long-term therapy for a patient with uncontrolled asthma or as a short ‘rescue’ course at any stage for acute exacerbation.

Long-term oral corticosteroid therapy may be required to control severe persistent asthma, but its use is limited by the risk of significant adverse effects. In these cases high-dose inhaled corticosteroids should be continued so that oral requirements are reduced to a minimum. Oral doses should be given as a single dose in the morning to reduce the disturbance to the circadian cortisol secretion. Dosage should always be adjusted to the lowest dose which controls symptoms.
**Sodium cromoglicate**

*Sodium cromoglicate* prevents the asthmatic response to certain allergic and nonallergic stimuli. It may be used as long-term therapy early in the course of asthma. It reduces symptoms and the frequency of exacerbations and allows dosage reduction of bronchodilators and oral corticosteroids. Prophylaxis with sodium cromoglicate is generally less effective in adults than prophylaxis with inhaled corticosteroids, but long-term use of inhaled corticosteroids may be associated with more adverse effects. Sodium cromoglicate is of value in the prevention of exercise-induced asthma, a single dose being inhaled 30 minutes beforehand. Sodium cromoglicate is of no value for the treatment of acute attacks of asthma. In general, sodium cromoglicate produces only minimal adverse effects such as occasional coughing upon inhalation of the powder formulation.

**Anticholinergic (antimuscarinic) bronchodilators**

*Ipratropium* can provide short-term relief in chronic asthma, but short-acting beta2-agonists work more quickly. Ipratropium is also used as a bronchodilator in chronic obstructive pulmonary disease.

**Salbutamol**

Salbutamol is a representative beta2-adrenoceptor agonist. Various drugs can serve as alternatives

*Tablets*, salbutamol (as sulfate) 2 mg, 4 mg

*Syrup*, salbutamol (as sulfate) 2 mg/5 ml

*Injection* (Solution for injection), salbutamol (as sulfate) 50 micrograms/ml, 5-ml ampoule

*Aerosol inhalation* (Pressurized inhalation), salbutamol (as sulfate) 100 micrograms/metered inhalation

*Nebulizer solution*, salbutamol (as sulfate) 5 mg/ml, 20-ml ampoules

**Uses:**

prophylaxis and treatment of asthma; premature labour (section 22.1)

**Precautions:**

hyperthyroidism, myocardial insufficiency, arrhythmias, susceptibility to QT-interval prolongation, hypertension, pregnancy (but appropriate to use; see also notes above); breastfeeding (Appendix 3); diabetes mellitus—especially intravenous administration (monitor blood glucose; ketoacidosis reported); **interactions**: Appendix 1

**Dosage:**
Chronic asthma (when inhalation is ineffective), **by mouth**, **ADULT** 2–4 mg 3 or 4 times daily; in some patients up to maximum of 8 mg 3 or 4 times daily; **CHILD** under 2 years, 100 micrograms/kg 4 times daily, 2–6 years, 1–2 mg 3–4 times daily, 6–12 years, 2 mg 3–4 times daily

Severe acute bronchospasm, **by slow intravenous injection**, **ADULT** 250 micrograms, repeated if necessary

Relief of acute bronchospasm, **by aerosol inhalation**, **ADULT** 100–200 micrograms (1–2 puffs); **CHILD** 100 micrograms (1 puff) increased to 200 micrograms (2 puffs) if necessary; **by intramuscular or subcutaneous injection**, **ADULT** 500 micrograms repeated every 4 hours if necessary

Prophylaxis of exercise-induced bronchospasm, **by aerosol inhalation**, **ADULT** 200 micrograms (2 puffs); **CHILD** 100 micrograms (1 puff) increased to 200 micrograms (2 puffs) if required

Chronic asthma (as adjunct in stepped treatment), **by aerosol inhalation**, **ADULT** 100–200 micrograms (1–2 puffs) up to 3–4 times daily; **CHILD** 100 micrograms (1 puff) 3–4 times daily, increased to 200 micrograms (2 puffs) 3–4 times daily if necessary

Severe acute asthma or chronic bronchospasm unresponsive to conventional treatment, **by inhalation of nebulized solution**, **ADULT** and **CHILD** over 18 months, 2.5 mg repeated up to 4 times daily; may be increased to 5 mg if necessary—medical assessment should be considered since alternative therapy may be indicated; **CHILD** under 18 months, clinical efficacy uncertain (transient hypoxaemia may occur—consider oxygen supplementation)

**Adverse effects:**

hypokalaemia after high doses (see notes above); arrhythmias, tachycardia, palpitations, peripheral vasodilation, fine tremor (usually hands), muscle cramps, headache, insomnia, behavioural disturbances in children; hypersensitivity reactions including paradoxical bronchospasm, urticaria and angioedema; slight pain on intramuscular injection

**Beclometasone dipropionate**

Beclometasone dipropionate is a representative corticosteroid. Various drugs can serve as alternatives

**Aerosol inhalation** (Pressurized inhalation), beclometasone dipropionate 50 micrograms/metered inhalation (standard dose inhaler), 250 micrograms/metered inhalation (high dose inhaler)

**Uses:**

chronic asthma not controlled by short-acting beta₂ -adrenoceptor agonists
Precautions:

see notes above; active or quiescent tuberculosis; systemic therapy may be required during periods of stress or when airway obstruction or mucus prevent drug access to smaller airways; not for relief of acute symptoms; monitor height of children receiving prolonged treatment—if growth slowed, review therapy

Dosage:

Chronic asthma, by aerosol inhalation (standard dose inhaler), ADULT 200 micrograms twice daily or 100 micrograms 3–4 times daily (in more severe cases, initially 600–800 micrograms daily); CHILD 50–100 micrograms 2–4 times daily or 100–200 micrograms twice daily

Chronic asthma, by aerosol inhalation (high dose inhaler), ADULT 500 micrograms twice daily or 250 micrograms 4 times daily; if necessary may be increased to 500 micrograms 4 times daily; CHILD not recommended

Adverse effects:

oropharyngeal candidosis, cough and dysphonia (usually only with high doses); adrenal suppression, growth retardation in children and adolescents, impaired bone metabolism, glaucoma and cataract (with high doses, but less frequent than with systemic corticosteroids); paradoxical bronchospasm—requires discontinuation and alternative therapy (if mild, may be prevented by inhalation of beta₂-adrenoceptor agonist or by transfer from aerosol to powder inhalation); rarely, urticaria, rash, angioedema

Candidosis. Candidosis can be reduced by use of a spacing device (see notes above); rinsing the mouth with water after inhalation may help to prevent candidosis

Theophylline and Aminophylline

Aminophylline is a representative xanthine bronchodilator. Various drugs including theophylline can serve as alternatives

Tablets, theophylline 100 mg

Modified-release tablets, theophylline 200 mg, 300 mg

Injection (Solution for injection), aminophylline 25 mg/ml, 10-ml ampoule

Uses:

chronic asthma including nocturnal asthma; acute severe asthma

Contraindications:

porphyria; known hypersensitivity to ethylenediamine (for aminophylline)
**Precautions:**

cardiac disease, hypertension, hyperthyroidism, peptic ulcer, epilepsy, hepatic impairment (Appendix 5), pregnancy (Appendix 2), breastfeeding (Appendix 3), elderly, fever; smokers may require larger or more frequent doses; **interactions:** Appendix 1

**Dosage:**

Chronic asthma, *by mouth* (as tablets), **ADULT** and **CHILD** over 12 years, 100–200 mg 3–4 times daily after food; *by mouth* (as modified-release tablets) **ADULT** 300–450 mg every 12 hours

Nocturnal asthma, *by mouth* (as modified-release tablets), **ADULT** total daily requirement as single evening dose

*Note.* Plasma theophylline concentration for optimum response 10–20 mg/litre (55–110 micromol/litre); narrow margin between therapeutic and toxic dose; see notes above; a range of 5–15 mg/litre (27.5–82.5 micromol/litre) may be effective and associated with fewer adverse effects

Acute severe asthma (not previously treated with theophylline), *by slow intravenous injection* (over at least 20 minutes), **ADULT** and **CHILD** 5 mg/kg; maintenance, *by intravenous infusion*, **ADULT** 500 micrograms/kg/hour; **CHILD** 6 months–9 years, 1 mg/kg/hour, 10–16 years, 800 micrograms/kg/hour, adjusted according to plasma-theophylline concentration

*Note.* Patients taking oral theophylline (or aminophylline) should not normally receive intravenous aminophylline unless plasma-theophylline concentration is available to guide dosage

**Adverse effects:**

nausea and other gastrointestinal disturbances, restlessness, anxiety, tremor, palpitations, headache, insomnia, dizziness; convulsions, arrhythmias and hypotension—especially if given by rapid injection; urticaria, erythema and exfoliative dermatitis—resulting from hypersensitivity to ethylenediamine component of aminophylline

**Sodium cromoglicate**

Sodium cromoglicate is a representative antiasthma drug. Various drugs can serve as alternatives

Sodium cromoglicate is a complementary drug

*Aerosol inhalation* (Pressurized inhalation), sodium cromoglicate 5 mg/metered inhalation

**Uses:**
prophylaxis of asthma; prevention of exercise-induced asthma

**Precautions:**

pregnancy (appropriate to use; see notes above and Appendix 2); breastfeeding (Appendix 3)

**Dosage:**

Prophylaxis of asthma and exercise-induced asthma, by aerosol inhalation, **ADULT** and **CHILD** 10 mg 4 times daily, increased in severe cases or during periods of risk to 6–8 times daily; additional doses may be taken before exercise; when stabilized, may be possible to reduce to maintenance of 5 mg 4 times daily

**Adverse effects:**

coughing, transient bronchospasm

**Ipratropium bromide**

_Aerosol inhalation_ (Pressurized inhalation), ipratropium bromide 20 micrograms/metered dose

**Uses:**

chronic asthma; chronic obstructive pulmonary disease

**Precautions:**

prostatic hypertrophy; pregnancy; glaucoma (standard doses unlikely to be harmful; reported with nebulized drug, particularly in association with nebulized salbutamol)

**Dosage:**

Chronic asthma or chronic obstructive pulmonary disease, by aerosol inhalation, **ADULT** 20–40 micrograms, in early treatment up to 80 micrograms at a time, 3–4 times daily; **CHILD** up to 6 years, 20 micrograms 3 times daily, 6–12 years, 20–40 micrograms 3 times daily

**Adverse effects:**

occasionally, dry mouth; rarely, urinary retention, constipation