sive to maximal doses of bronchodilators and oral corticosteroids, (a point supported in children[4] but not in adults[5] by systematic review) whereas US guidelines do not consider xanthines have any benefit over the optimal use of beta agonists and consequently do not recommend their use (see p.1108).

1. Wang Y, *et al.* Comparison of inhaled corticosteroid combined with theophylline and double-dose inhaled corticosteroid in moderate to severe asthma. *Respirology* 2005; **10:** 189–95.
2. Lim S, *et al.* Comparison of high dose inhaled steroids, low dose inhaled steroids plus low dose theophylline, and low dose inhaled steroids alone in chronic asthma in general practice. *Thorax* 2000; **55:** 837–41.
3. Tee AKH, *et al.* Long acting beta-agonists versus theophylline for maintenance treatment of asthma. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 19/03/08).
4. Mitra A, *et al.* Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 19/03/08).
5. Parameswaran K, *et al.* Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 19/03/08).

Cardiac arrhythmias. Theophylline has been tried in various bradyarrhythmias, usually when other treatment has failed or is contra-indicated.[1-6] It appears to be of little value in bradyasystolic cardiac arrest.[7,8]

1. Viskin S, *et al.* Aminophylline for bradyasystolic cardiac arrest refractory to atropine and epinephrine. *Ann Intern Med* 1993; **118:** 279–81.
2. Sra JS, *et al.* Comparison of cardiac pacing with drug therapy in the treatment of neurocardiogenic (vasovagal) syncope with bradycardia or asystole. *N Engl J Med* 1993; **328:** 1085–90.
3. Bertolet BD, *et al.* Theophylline for the treatment of atrioventricular block after myocardial infarction. *Ann Intern Med* 1995; **123:** 509–11.
4. Alboni P, *et al.* Effects of permanent pacemaker and oral theophylline in sick sinus syndrome: the THEOPACE study: a randomized controlled trial. *Circulation* 1997; **96:** 260–6.
5. Ling CA, Crouch MA. Theophylline for chronic symptomatic bradycardia in the elderly. *Ann Pharmacother* 1998; **32:** 837–9.
6. Cawley MJ, *et al.* Intravenous theophylline — an alternative to temporary pacing in the management of bradycardia secondary to AV nodal block. *Ann Pharmacother* 2001; **35:** 303–7.
7. Abu-Laban RB, *et al.* Aminophylline in bradyasystolic cardiac arrest: a randomised placebo-controlled trial. *Lancet* 2006; **367:** 1577–84.
8. Hayward E, *et al.* Aminophylline in bradyasystolic cardiac arrest. *Emerg Med J* 2007; **24:** 582–3.

Cheyne-Stokes respiration. Oral theophylline considerably reduced Cheyne-Stokes respiration (periodic breathing) and episodes of central apnoea in 2 studies in patients with stable heart failure and left ventricular systolic dysfunction.[1,2] This was associated with an improvement in arterial-oxygen saturation during sleep. One study[1] observed no significant change in cardiac function, although pulmonary function did improve. Theophylline was also effective in a patient with Cheyne-Stokes respiration possibly related to diabetic autonomic neuropathy[3] (the use of the term Cheyne-Stokes respiration to describe this patient's respiratory disorder has been questioned[4,5]).

1. Javaheri S, *et al.* Effect of theophylline on sleep-disordered breathing in heart failure. *N Engl J Med* 1996; **335:** 562–7.
2. Hu K, *et al.* The effect of theophylline on sleep-disordered breathing in patients with stable chronic congestive heart failure. *Chin Med J* 2003; **116:** 1711–16.
3. Pesek CA, *et al.* Theophylline therapy for near-fatal Cheyne-Stokes respiration: a case report. *Ann Intern Med* 1999; **130:** 427–30.
4. Sin DD, Bradley TD. Theophylline therapy for near-fatal Cheyne-Stokes respiration. *Ann Intern Med* 1999; **131:** 713.
5. Geigel EJ, Chediak AD. Theophylline therapy for near-fatal Cheyne-Stokes respiration. *Ann Intern Med* 1999; **131:** 713–14.

Chronic obstructive pulmonary disease. In the treatment of chronic obstructive pulmonary disease (p.1112), the bronchodilators of first choice are usually either an antimuscarinic such as ipratropium bromide, or a $beta_2$ agonist such as salbutamol, given by inhalation. However the addition of an oral xanthine such as theophylline may be of value in some patients to maximise respiratory function and for its positive cardiac inotropic effects.

A systematic review[1] of studies comparing oral theophylline with placebo in patients with moderate to severe chronic obstructive pulmonary disease (COPD), found that theophylline treatment improved lung function, ventilatory capacity, and arterial blood gas tensions. A decrease in thoracic gas entrapment and hyperinflation, and an increase in respiratory muscle function and diaphragmatic strength could be responsible for the improvement in symptoms. Improvements in arterial blood gas tensions may result from an increased tidal volume caused by either a direct positive inotropic effect on the respiratory muscles, or a central stimulatory action, or both. The authors concluded that theophylline produced an improvement in lung function similar to that reported for long acting $beta_2$ agonists in COPD patients, and that with close monitoring beneficial effects may be obtained from theophylline therapy in those patients who remain symptomatic from COPD despite first-line bronchodilator therapy. Theophylline has been reported to exert an inhibitory effect on airway inflammation in COPD, particularly at plasma concentrations below 10 micrograms/mL.[2] It has also been suggested that low-dose theophylline may restore corticosteroid responsiveness in COPD patients, but further research is required to assess its role.

1. Ram FSF, *et al.* Oral theophylline for chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 19/03/08).
2. Barnes PJ. Theophylline for COPD. *Thorax* 2006; **61:** 742–4.

Contrast nephropathy. For mention of theophylline as a potential protectant against kidney damage induced by iodinated contrast media, see Effects on the Kidneys, under Amidotrizoic Acid, p.1476.

ECT. For mention of the use of theophylline as an adjunct to electroconvulsive therapy, see under Precautions, above.

Erythrocytosis. When pharmacological treatment is required for secondary erythrocytosis (p.1198), current UK guidelines[1,2] recommend an ACE inhibitor or an angiotensin II receptor antagonist as the usual drugs of first choice. Although theophylline appears to be less effective than an ACE inhibitor in post-transplantation erythrocytosis[3] an oral daily dose of 8 mg/kg has produced beneficial effects.[4,5] Theophylline may be of use given either alone or with an ACE inhibitor in those who fail to respond to first-line therapy. Theophylline treatment may also reduce erythrocytosis associated with chronic obstructive pulmonary disease.[6]

1. McMullin MF, *et al.* General Haematology Task Force of the British Committee for Standards in Haematology. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. *Br J Haematol* 2005; **130:** 174–95. Also available at: http://www.bcshguidelines.com/pdf/polycythaemia_05.pdf (accessed 19/03/08)
2. McMullin MF, *et al.* National Cancer Research Institute, Myeloproliferative Disorder Subgroup. British Committee for Standards in Haematology. Amendment to the guideline for diagnosis and investigation of polycythaemia/erythrocytosis. *Br J Haematol* 2007; **138:** 821–2. Also available at: http://www.bcshguidelines.com/pdf/polycythaemia_amendment_07.pdf (accessed 19/03/08)
3. Ok E, *et al.* Comparison of the effects of enalapril and theophylline on polycythemia after renal transplantation. *Transplantation* 1995; **59:** 1623–45.
4. Bakris GL, *et al.* Effects of theophylline on erythropoietin production in normal subjects and in patients with erythrocytosis after renal transplantation. *N Engl J Med* 1990; **323:** 86–90.
5. Ilan Y, *et al.* Erythrocytosis after renal transplantation: the response to theophylline treatment. *Transplantation* 1994; **57:** 661–4.
6. Oren R, *et al.* Effect of theophylline on erythrocytosis in chronic obstructive pulmonary disease. *Arch Intern Med* 1997; **157:** 1474–8.

Methotrexate neurotoxicity. For reference to the use of aminophylline or theophylline to relieve the acute neurotoxicity of methotrexate, see Other Drugs, under Treatment of Adverse Effects, p.747.

Perinatal asphyxia. Perinatal asphyxia frequently results in damage to the kidneys;[1] vasomotor nephropathy or acute renal failure may develop as a result of decreased perfusion to the kidneys.[2] Theophylline has been studied for the prevention of renal dysfunction associated with perinatal asphyxia in both term and preterm neonates.[1-3] Beneficial effects have been observed after early use of intravenous theophylline, including significant decreases in serum creatinine[1-3] and urinary β2-microglobulin (an indicator of tubular performance),[1,3] and a significant increase in creatinine clearance.[1-3] A single dose of 8 mg/kg theophylline, by slow intravenous injection in the first hour of life, was given to neonates at term.[1,3] Lower doses were used for preterm neonates; 1 mg/kg daily for 3 consecutive days.[2]

1. Bhat MA, *et al.* Theophylline for renal function in term neonates with perinatal asphyxia: a randomised, placebo-controlled trial. *J Pediatr* 2006; **149:** 180–4.
2. Cattarelli D, *et al.* A randomised, double blind, placebo controlled trial of the effect of theophylline in prevention of vasomotor nephropathy in very preterm neonates with respiratory distress syndrome. *Arch Dis Child Fetal Neonatal Ed* 2006; **91:** F80–F84.
3. Jenik AG, *et al.* A randomized, double-blind, placebo-controlled trial of the effects of prophylactic theophylline on renal function in term neonates with perinatal asphyxia. *Pediatrics* 2000; **105:** e45. Also available at: http://pediatrics.aappublications.org/cgi/content/full/105/4/e45 (accessed 19/03/08)

Preparations

BP 2008: Prolonged-release Theophylline Tablets;
USP 31: Theophylline and Guaifenesin Capsules; Theophylline and Guaifenesin Oral Solution; Theophylline Capsules; Theophylline Extended-release Capsules; Theophylline in Dextrose Injection; Theophylline Oral Solution; Theophylline Sodium Glycinate Elixir; Theophylline Sodium Glycinate Tablets; Theophylline Tablets; Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Aminofilin†; Asmabiol†; Crisasma; Drilyna; Nefoben; Teodosis; Teosona; Teosona Sol; Theo-Dur†; ***Austral.:*** Nuelin; ***Austria:*** Aerodyne†; Afonilum; Euphyllin; Respicur; Theoplus; Theospirex; Unifyl; ***Belg.:*** Euphyllin; Theo-2; Theolair; Xanthium; ***Braz.:*** Bermacia†; Codrinan; Talofilina; Teofilab; Teolong; Teophyl; Teoston; ***Canad.:*** Apo-Theo; Novo-Theophyl; Quibron-T†; Theo-Dur†; Theolair; Uniphyl; ***Chile:*** Elixine; ***Cz.:*** Afonilum; Euphyllin; Euphylong†; Spophyllin; Teotard†; Theo-Dur†; Theophyllard†; Theoplus; Uni-Dur†; Unilair†; ***Denm.:*** Nuelin; Pulmo-Timelets; Theo-Dur; UniXan; Uno-Lin†; ***Fin.:*** Euphyllin†; Nuelin; Retafyllin; Theo-Dur†; Theofol; ***Fr.:*** Euphylline; Theostat; Xanthium†; ***Ger.:*** Aerobin; Afonilum; Afonilum novo; afpred-THEO; Bronchoparat; Bronchoretard; Contiphyllin; Cronasma†; duraphyllin; Euphylong; Pulmidur†; Pulmo-Timelets; Solosin; Theo; Theolair†; Tromphyllin; Unilair; Uniphyllin; ***Gr.:*** Aberten; Mediphyllin Chrono; Novaphylline†; Theo-Bros; Theo-Dur; Theoplus; Uniphyllin; ***Hong Kong:*** CP-Theo; Euphylong; Novo-Theophyl†; Nuelin; Slo-Theo; Theo-Dur†; Theotrim; ***Hung.:*** Egifilin; Euphylong; Retafyllin; Theophtard; Theospirex; ***India:*** Phylobid; Phyloday; Theo PA; Theobid; Theoday; Theoped; Unicontin; ***Indon.:*** Bronchophylin; Brondilex; Bronsolvan; Euphyllin; Quibron-T; Retaphyl; Theobron; ***Irl.:*** Nuelin; Slo-Phyllin; Uniphyllin Continus; Zepholin; ***Israel:*** Glyphyllin; Theotard; Theotrim; ***Ital.:*** Aminomal; Diffumal; Euphyllina; Frivent; Paidomal; Respicur; Tefamin; Theo-24; Theo-Dur; Theolair; ***Jpn:*** Theodur; Theolong; ***Malaysia:*** Apo-Theo; Nuelin; Numalin†; Retafyllin; Theolin†; ***Mex.:*** Apoteoprol†; Elixofilina; Fluidasa; Pharmafil; Slo-Bid†; Teolong†; Uni-Dur†; ***Neth.:*** Euphylong; Theolair; ***Norw.:*** Nuelin; Theo-Dur; ***NZ:*** Nuelin; ***Philipp.:*** Asmasolon; Brondil (Reformulated); Nuelin; Phenedrine; Theo-Dur; ***Pol.:*** Afonilum; Euphyllin; Theoplus; Theospirex; Theovent; ***Port.:*** Eufilina; Lepobron†; Teonibsa†; Teovent†; Unicontin; ***Rus.:*** Teotard (Теотард); ***S.Afr.:*** Alcophyllin; Chronophyllin†; Euphyllin; Microphyllin; Nuelin; Pulmophyllin; Theoplus; Uniphyl; ***Singapore:*** Apo-Theo; Nuelin; Retafyllin†; Theolin; Theoplus†; Xanthium†; ***Spain:*** Chantaline†; Elixifilin; Eufilina; Histafilin; Pulmeno; Teolixir; Teromol; Theo Max†; Theo-Dur; Theolair; Theoplus; Unilong†; Vent Retard†; ***Swed.:*** Euphylong†; Theo-Dur; ***Switz.:*** Euphyllin; Sodip-phylline†; Theolair; Unifyl; ***Thai.:*** Aerobin†; Almarion; Asmasolon; Bronoday; Franol; Med-Phylline†; Nuelin; Retafyllin; Temaco; Theotrim; Xanthium; ***Turk.:*** Bronkolin; Pirasmin; Talotren; Teobag; Teokap; Teosel; Theo-Dur; Xanthium; ***UAE:*** Theophar; ***UK:*** Nuelin; Slo-Phyllin; Uniphyllin Continus; ***USA:*** Accurbron; Aerolate; Aquaphyllin†; Asmalix; Elixomin†; Elixophyllin; Quibron-T†; Respbid†; Slo-Bid; Slo-Phyllin; Sustaire†; T-Phyl; Theo-24; Theo-X†; Theochron; Theoclear†; Theolair; Theovent†; Uniphyl; ***Venez.:*** Nuelin; Teobid.

Multi-ingredient: ***Arg.:*** Airbronal†; Bronkasma†; Dexa Aminofilin; Dexa Teosona; Fatigan Bronquial†; Inastmol†; Sedacris; ***Austria:*** Ambredin; Asthma 23 D; ***Braz.:*** Abacateirol†; Alergotox†; Asmatiron†; Bronquitos; Endotussin; Franol; Marax; ***Canad.:*** ratio-Theo-Bronc; ***Cz.:*** Oxantil; ***Fin.:*** Theofol Comp; ***Fr.:*** Hypnasmine†; ***Ger.:*** Broncho-Euphyllin; ***Gr.:*** Gulamyl; ***India:*** Alergin; Asmapax; Asthmino†; Broncofol-P†; Broncofol†; Dericip; Dericip Plus; Deriphyllin; Etyofil†; Marax; Tergil-T; Theo-Asthalin; Theobric; ***Indon.:*** Asmadex; Asmano; Asmasolon; Asthma Soho; Neo Napacin; Prinasma; Teosal; Theochodil; Tusapres; ***Irl.:*** Franol Expectorant†; ***Malaysia:*** Asthma; Brondal†; Grenin†; Theophylline Expectorant; ***Mex.:*** Aminoefedrison; ***Philipp.:*** Mucophylline; ***Pol.:*** Baladex; ***Port.:*** Cosmaxil†; Prelus†; ***S.Afr.:*** Actophlem; Alcophyllex; Diatussin; Metaxol; Solphyllex; Solphyllin; Theophen; Theophen Comp; ***Spain:*** Novofilin†; Teolixir Compositum; ***Thai.:*** Almasal; Asiabron; Bronchil; Brondil; Mila-Asma; Polyphed; Qualiton; ***UK:*** Do-Do ChestEze; Franol Plus†; Franol†; ***USA:*** Elixophyllin-GG; Elixophyllin-KI; Glyceryl-T; Hydrophed; Marax; Neoasma; Quadrinal; Quibron†; Slo-Phyllin GG†; Tedrigen; Theodrine; Theomax DF; ***Venez.:*** Marax†; Metilfedrin†; Metoxifilin; Teofedril†.

Tiotropium Bromide *(BAN, rINN)*

Ba-679; Ba-679BR; Bromuro de tiotropio; Tiotropii bromidum; Tiotropium, bromure de; Tiotropyum Bromür. 6β,7β-Epoxy-3β-hydroxy-8-methyl-1α*H*,5α*H*-tropanium bromide di-2-thienylglycolate.

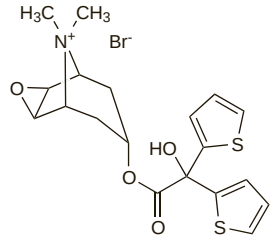
Тиотропия Бромид

$C_{19}H_{22}BrNO_4S_2$ = 472.4.

CAS — 186691-13-4 (tiotropium); 139404-48-1 (anhydrous tiotropium bromide or tiotropium bromide hydrate); 136310-93-5 (anhydrous tiotropium bromide); 411207-31-3 (tiotropium bromide monohydrate).

ATC — R03BB04.

ATC Vet — QR03BB04.



Adverse Effects and Precautions

As for Ipratropium Bromide (p.1124).

Pharyngitis, sinusitis, rhinitis, and epistaxis have also been reported after inhalation.

Patients with moderate to severe renal impairment (creatinine clearance 50 mL/minute or less) should be closely monitored as tiotropium bromide is mainly excreted by the kidneys.

Effects on the cerebrovascular system. In March 2008 the FDA reported[1] that the manufacturer of tiotropium bromide (*Boehringer Ingelheim*) had informed them that they had identified a possible increased risk of stroke in patients taking tiotropium bromide. From pooled analysis of 29 clinical studies in patients with chronic obstructive pulmonary disease preliminary estimates of the risk of stroke were 8 per 1000 patients treated for

one year with tiotropium compared with 6 per 1000 patients given placebo for one year. The FDA had not yet confirmed the analyses and urged caution in interpreting these preliminary results.

1. FDA. Early communication about ongoing safety review of tiotropium (marketed as Spiriva HandiHaler) (issued 18th March 2008). Available at: http://www.fda.gov/cder/drug/early_comm/tiotropium.htm (accessed 22/05/08)

Effects on the skin. Subacute cutaneous lupus erythematosus has been reported in a patient inhaling tiotropium.[1] Skin lesions developed one week after introduction of the drug, resolved when the drug was stopped, and recurred on rechallenge.

Inhaled tiotropium has also been associated with a photosensitive lichenoid eruption in another patient,[2] 22 months after starting treatment. The lesions resolved when the drug was stopped; patch testing however, gave a negative result. Rechallenge was not attempted.

1. Pham H-C, Saurat J-H. Inhalation route inducing subacute cutaneous lupus erythematosus with tiotropium. *Arch Dermatol* 2005; **141:** 911–12.
2. Pérez-Pérez L, *et al.* Photosensitive lichenoid eruption and inhaled tiotropium bromide. *Dermatology* 2007; **214:** 97–8.

Interactions

For interactions associated with antimuscarinics in general, see Atropine, p.1220. However, these interactions are not usually seen with antimuscarinics, such as tiotropium, given by inhalation.

Pharmacokinetics

After inhalation, some tiotropium bromide is absorbed from the lung, with the majority deposited in the gastrointestinal tract. In healthy subjects a systemic bioavailability of about 20% is reported after dry powder inhalation, and about 33% after inhalation of the solution. Tiotropium is about 72% bound to plasma proteins. It is excreted largely unchanged in the urine, although it may undergo some metabolism by non-enzymatic cleavage and by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. The terminal elimination half-life is between 5 and 6 days.

Uses and Administration

Tiotropium bromide is a quaternary ammonium antimuscarinic that is structurally related to ipratropium but has a prolonged bronchodilator action. It is used similarly to ipratropium (p.1124) in the maintenance treatment of reversible airways obstruction, as in chronic obstructive pulmonary disease (below); tiotropium is not suitable for the initial treatment of acute bronchospasm. Tiotropium bromide can be given as inhalation powder in capsules containing 22.5 micrograms of tiotropium bromide monohydrate, equivalent to 18 micrograms of tiotropium, and supplying 10 micrograms of tiotropium from the mouthpiece of the inhaler device. The contents of one capsule are inhaled daily, at the same time each day.

Tiotropium bromide can also be given as inhalation solution via a metered-dose inhaler. Each metered dose contains 3.124 micrograms of tiotropium bromide monohydrate equivalent to 2.5 micrograms of tiotropium. Two doses of 2.5 micrograms are inhaled daily, at the same time each day.

◊ References.

1. Hvizdos KM, Goa KL. Tiotropium bromide. *Drugs* 2002; **62:** 1195–1203.

Chronic obstructive pulmonary disease. In chronic obstructive pulmonary disease (COPD; p.1112) tiotropium bromide has been shown to be effective at improving dyspnoea,[1-3] health-related quality of life,[1,3] symptom-limited exercise tolerance,[2] lung function measurements,[3] and reducing exacerbations[1,3,4] compared with placebo.

Tiotropium has also been found to be more effective than ipratropium at improving dyspnoea, health-related quality of life,[5] and lung function,[5,6] and reducing exacerbations;[5] consideration of tiotropium as first-line maintenance treatment in COPD has been suggested.

Similarly, tiotropium has produced better bronchodilatation, reduced dyspnoea, and improved health-related quality of life scores compared with salmeterol.[7]

Combining tiotropium therapy with an inhaled corticosteroid and a long-acting beta$_2$ agonist did not statistically influence rates of COPD exacerbations but did improve lung function, quality of life, and hospitalisation rates in patients with moderate to severe COPD.[8]

A systematic review[9] and a meta-analysis[10] confirmed that tiotropium reduces exacerbations and related hospitalisations, improves quality of life and symptoms in stable COPD. Tiotropium may also have slowed the decline in forced expiratory volume (FEV) seen in COPD; however, the authors concluded that further studies are required to evaluate the effect of tiotropium on FEV and to clarify its role in relation to long-acting beta$_2$ agonists.

The role of tiotropium in the management of COPD has been extensively reviewed.[11-14]

1. Casaburi R, *et al.* A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002; **19:** 217–24.
2. Maltais F, *et al.* Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. *Chest* 2005; **128:** 1168–78.
3. Brusasco V, *et al.* Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax* 2003; **58:** 399–404.
4. Niewoehner DE, *et al.* Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med* 2005; **143:** 317–26.
5. Vincken W, *et al.* Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. *Eur Respir J* 2002; **19:** 209–16.
6. van Noord JA, *et al.* A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease. *Thorax* 2000; **55:** 289–94.
7. Donohue JF, *et al.* A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 2002; **122:** 47–55.
8. Aaron SD, *et al.* Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2007; **146:** 545–55.
9. Barr RG, *et al.* Tiotropium for stable chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 18/02/08).
10. Barr RG, *et al.* Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis. *Thorax* 2006; **61:** 854–62. Correction. *ibid.*; **62:** 191.
11. Gross NJ. Tiotropium bromide. *Chest* 2004; **126:** 1946–53.
12. Olin JL. Tiotropium: an inhaled anticholinergic for chronic obstructive pulmonary disease. *Am J Health-Syst Pharm* 2005; **62:** 1263–9.
13. Somand H, Remington TL. Tiotropium: a bronchodilator for chronic obstructive pulmonary disease. *Ann Pharmacother* 2005; **39:** 1467–75.
14. Burns G, Bianchi S. Chronic obstructive pulmonary disease: the evidence for use of tiotropium. *Br J Hosp Med* 2006; **67:** 85–91.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Spiriva; ***Austral.:*** Spiriva; ***Austria:*** Spiriva; ***Belg.:*** Spiriva; ***Braz.:*** Spiriva; ***Canad.:*** Spiriva; ***Chile:*** Spiriva; ***Cz.:*** Spiriva; ***Denm.:*** Spiriva; ***Fin.:*** Spiriva; ***Fr.:*** Spiriva; ***Ger.:*** Spiriva; ***Gr.:*** Spiriva; ***Hong Kong:*** Spiriva; ***Hung.:*** Spiriva; ***India:*** Tiova; ***Indon.:*** Spiriva; ***Irl.:*** Spiriva; ***Israel:*** Spiriva; ***Ital.:*** Spiriva; ***Jpn:*** Spiriva; ***Malaysia:*** Spiriva; ***Mex.:*** Spiriva; ***Neth.:*** Spiriva; ***Norw.:*** Spiriva; ***NZ:*** Spiriva; ***Philipp.:*** Spiriva; ***Pol.:*** Spiriva; ***Port.:*** Spiriva; ***Rus.:*** Spiriva (Спирива); ***S.Afr.:*** Spiriva; ***Singapore:*** Spiriva; ***Spain:*** Spiriva; ***Swed.:*** Spiriva; ***Switz.:*** Spiriva; ***Thai.:*** Spiriva; ***Turk.:*** Spiriva; ***UK:*** Spiriva; ***USA:*** Spiriva; ***Venez.:*** Spiriva.

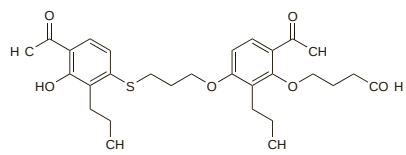
Multi-ingredient: ***India:*** Duova.

Tipelukast *(USAN, rINN)*

KCA-757; MN-001; Tipélukast; Tipelukastum. 4-(6-Acetyl-3-{3-[(4-acetyl-3-hydroxy-2-propylphenyl)sulfanyl]propoxy}-2-propylphenoxy)butanoic acid.

Типелукаст

$C_{29}H_{38}O_7S$ = 530.7.
CAS — 125961-82-2.



Profile

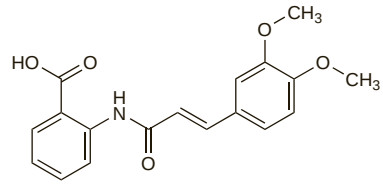
Tipelukast is a leukotriene receptor antagonist (p.1108), a phosphodiesterase inhibitor, and 5-lipoxygenase inhibitor that is under investigation for the treatment of asthma.

Tranilast *(USAN, rINN)*

MK-341; N-5′; Tranilastum. *N*-(3,4-Dimethoxycinnamoyl)anthranilic acid.

Траниласт

$C_{18}H_{17}NO_5$ = 327.3.
CAS — 53902-12-8.



Adverse Effects and Precautions

Adverse effects reported with tranilast have included gastrointestinal disturbances, headache, drowsiness or insomnia, dizziness, malaise, and skin rashes and generalised pruritus. Rarely, liver function disturbance or jaundice, renal dysfunction, cystitis-like symptoms, anaemia, leucopenia, thrombocytopenia, palpitations, oedema, facial flushing, and stomatitis may occur. Tranilast should be used with caution in patients with impaired hepatic or renal function. Haematological monitoring is recommended.

Irritation and blepharitis have been reported after topical application to the eye.

Licensed product information advises against the use of tranilast in pregnancy because of teratogenicity in *animal* studies.

Tranilast should not be used for the treatment of acute asthma attacks. The general cautions described under sodium cromoglicate (p.1136) also apply.

Uses and Administration

Tranilast has a stabilising action on mast cells resembling that of sodium cromoglicate (p.1137). It is also stated to inhibit collagen synthesis in fibroblasts. It is used in the prophylactic management of asthma (p.1108) and in allergic rhinitis (p.565), conjunctivitis (p.564), and eczema (p.1579). It is also used in the management of keloids and hypertrophic scarring. The usual oral adult dose is 100 mg three times daily. For details of doses in children, see below. Eye drops containing tranilast 0.5% are used four times daily for allergic conjunctivitis.

Tranilast has been investigated for the prevention of restenosis after coronary artery revascularisation procedures but was found to be ineffective.

Administration in children. Tranilast is given to children for the prophylactic management of asthma, in allergic rhinitis and eczema, and in the management of keloids and hypertrophic scars. An oral daily dose of 5 mg/kg, given in 3 divided doses, may be used.

Sarcoidosis. For a mention of possible benefit from tranilast in cutaneous sarcoidosis, see p.1512.

Preparations

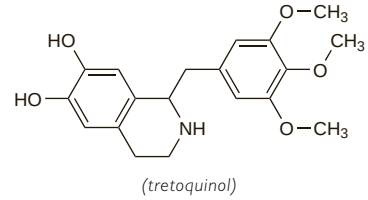
Proprietary Preparations (details are given in Part 3)
Jpn: Rizaben.

Tretoquinol Hydrochloride *(plNNM)* ⊗

AQ-110 (tretoquinol); Hidrocloruro de tretoquinol; Ro-07-5965; Trétoquinol, Chlorhydrate de; Tretoquinoli Hydrochloridum; Trimethoquinol Hydrochloride; Trimetoquinol Hydrochloride. (–)-1,2,3,4-Tetrahydro-1-(3,4,5-trimethoxybenzyl)isoquinoline-6,7-diol hydrochloride monohydrate.

Третохинола Гидрохлорид

$C_{19}H_{23}NO_5$,HCl,H_2O = 399.9.
CAS — 30418-38-3 (tretoquinol); 18559-59-6 (anhydrous tretoquinol hydrochloride).
ATC — R03AC09; R03CC09.
ATC Vet — QR03AC09; QR03CC09.



(tretoquinol)

Pharmacopoeias. In *Jpn.*

Profile

Tretoquinol is a direct-acting sympathomimetic reported to have a selective action on beta$_2$ receptors (a beta$_2$ agonist). It has properties similar to those of salbutamol (p.1131). It is given as the hydrochloride for its bronchodilating properties in the management of reversible airways obstruction, as in asthma (p.1108) or in some patients with chronic obstructive pulmonary disease (p.1112).

Preparations

Proprietary Preparations (details are given in Part 3)
Indon.: Inolin; ***Jpn:*** Inolin†.