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.

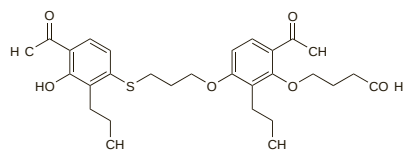
Multi-ingredient: ***India:*** Duova.

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

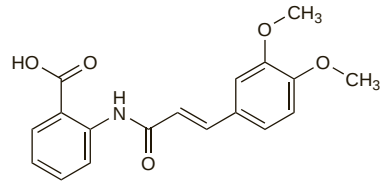
Tipelukast is a leukotriene receptor antagonist (p.1108), a phosphodiesterase inhibitor, and 5-lipoxygenase inhibitor that is under investigation for the treatment of asthma.

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

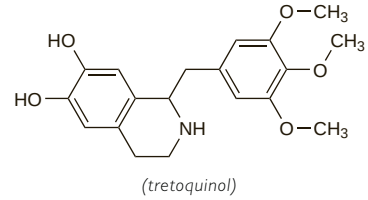
Proprietary Preparations (details are given in Part 3)
Jpn: Rizaben.

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†.