Commissioning Support
Tiotropium inhaler
(Spiriva Respimat 2.5 mcg®▼)

For the treatment of asthma

Commissioning guidance:

When making a decision about the use of tiotropium, commissioners may wish to consider the following:

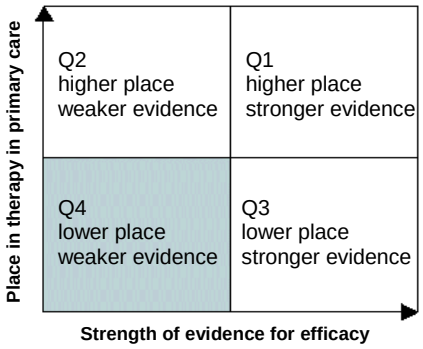
- That the licensed indications for this treatment place it at Step 4 in the BTS/SIGN guidance treatment pathway for asthma, and those patients with this level of disease severity or instability should be receiving regular reviews of their treatment.
- That arrangements are in place to enable appropriate and regular review of patients with asthma. The reviews should include:
  - Check of inhaler technique and discussion of potential trigger factors
  - Criteria for starting and stopping treatment
  - Review of cardiovascular risk factors in patients receiving inhaled anticholinergic medications
  - A review of treatment in patients receiving tiotropium,1 to 2 months following treatment initiation
- The MHRA advised in February[1] that the treatment of all patients already taking tiotropium should be reviewed as part of the comprehensive management plan to ensure that it remains appropriate for them; and that there should be regular review of treatment of patients at high risk of cardiovascular events.
- There is an additional drug acquisition cost associated with the use of tiotropium as an add-on treatment.

Prescribing guidance: Category A (Q4) **BNF: 3.2**

Tiotropium is suitable for prescribing in primary care for the treatment of asthma, within its licensed indications and emphasising that use of a LAMA is an option discussed at Step 4 of the BTS/SIGN guidance. It was the opinion of the committee that, given the severity of asthma at Step 4, consideration should be given to whether an opinion should be sought from a specialist or practitioner with a special interest in asthma before initiating an additional treatment.

Category A: Suitable for prescribing in primary care

Q4 rating: The evidence for efficacy for tiotropium was considered to be relatively weak; based on three RCTs that evaluated tiotropium within its licensed indications and reported patient-oriented outcomes. There is no evidence for comparative efficacy with other suitable treatments from this stage in the asthma treatment pathway, e.g. leukotriene antagonists or theophylline. It was specialist opinion that tiotropium was an option for treatment, following a trial of leukotriene antagonists and that at that stage of disease severity referral to specialist review may be a preferred option rather than an additional inhaled therapy.



The Q rating relates to the drug's position on the effectiveness indicator grid.
The strength of the evidence is determined by the quality and quantity of studies that show significant efficacy of the drug compared with placebo or alternative therapy. Its place in therapy in primary care takes into account safety and practical aspects of using the drug in primary care, alternative options, relevant NICE guidance, and the need for secondary care input.

Description of technology

Tiotropium is an inhaled long-acting muscarinic antagonist (LAMA; or anticholinergic) treatment. It is licensed for use in adult patients with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (ICS: ≥800 mcg budesonide/day or equivalent) and long-acting β_2-agonists and who experienced one or more severe exacerbations in the previous year.[2]

The recommended dose is 5 mcg tiotropium taken as 2 puffs, once daily.

Background

Asthma is a chronic inflammatory condition of the airways, the cause of which is not completely understood. In affected patients, the airways are hyper-responsive and constrict easily in response to a wide range of stimuli, including viral respiratory infections, exercise, smoke, cold, and allergens such as pollen, mould, animal fur and the house dust mite.[3,4] This may result in recurring episodes of wheezing, breathlessness, chest tightness and coughing.[4] About 5.4 million people in the UK are currently receiving treatment for asthma: 1.1 million children (1 in 11), and 4.3 million adults (1 in 12).[5]

In the BTS/SIGN guidance on asthma (updated 2014)[6], the use of a LAMA is referred to as part of the options for treatment at Step 4 of the treatment pathway, when the patients' asthma is not adequately controlled using a long-acting ß$_2$ agonist (LABA) plus

an optimal dose of ICS of at least 800 mcg beclometasone (or equivalent). At Stage 3/4 the additional options available are:

- Increase ICS dose up the to the equivalent of 2000 mcg of beclometasone dipropionate per day
- Add a leukotriene receptor antagonist (montelukast or zafirlukast)
- Add theophylline modified release
- Add a slow-release ß$_2$-agonist tablet (salbutamol)

Clinical evidence for efficacy and safety

Two replicate, 48-week, double-blind, randomised, placebo-controlled trials evaluated tiotropium treatment (5 mcg; 2 puffs, once daily) in 907 adults with poorly controlled asthma and persistent airflow obstruction (post-bronchodilator forced expiratory volume in one second [FEV_1] < 80% predicted normal) who were already treated with a ICS plus LABA.[7] Recent smokers or people with a diagnosis of COPD were excluded from the trials. Participants continued existing concomitant asthma treatments during the trial provided they were at stable dose; these included omalizumab (4% of patients), leukotriene antagonists (20-25%), theophylline (20%), antihistamines (15%) and oral steroids (4-7%). The co-primary outcome measures were peak (3-hours post-dose) and trough (pre-dose) FEV_1 after 24 weeks' treatment, and the time to first exacerbation after 48 weeks' treatment. Secondary outcomes included the Asthma control Questionnaire 7 (ACQ-7) and the Asthma Quality of Life Questionnaire (AQLQ).

In addition, a third cross-over, placebo-controlled RCT[8] (n = 107, 3 eight-week treatment periods) evaluated tiotropium at doses of 5 mcg or 10 mcg (2 puffs, once daily) in addition to the patients' current maintenance therapy (high dose ICS [>800mcg of budesonide or equivalent] + LABA). The inclusion criteria were as described above. The primary outcome was FEV_1; the mini-AQLQ was among the secondary outcomes.

Results

Lung function: after 24 weeks, there were significantly greater improvements in peak and trough FEV_1 in tiotropium-treated patients than with placebo treatment. The difference in peak FEV_1 response between tiotropium and placebo was 86mL and 154mL in trial 1 and trial 2, respectively. The difference in trough responses was 88mL and 111mL, respectively for the two, replicate trials. The cross-over trial[8] reported a peak FEV_1 response for the licensed tiotropium 5mcg dose *vs.* placebo of 139mL, and a trough FEV_1 response of 86mL after eight weeks' treatment.

Exacerbations: The time to first treatment exacerbation was 56 days longer with tiotropium treatment than with placebo (282 days *vs.* 226 days; hazard ratio 0.79 [95% CI 0.62 to 1.00]; p = 0.03). Significantly fewer tiotropium-treated patients experienced at least one severe exacerbation compared with those receiving placebo (26.9% *vs*. 32.8%; hazard ratio 0.79; p = 0.03).

Asthma control and quality of life: In the two replicate RCTs[7] results from these questionnaires were only significantly different for tiotropium compared with placebo in Trial 2. The minimum clinically important difference in scores between treatment groups was not achieved in either questionnaire in either trial 1 or trial 2. Similar results were reported for the mini-AQLQ in the cross-over trial.[8]

Adverse events

Adverse events were considered to be drug-related in 5.7% of tiotropium-treated participants and 4.6% of placebo-treated participants. Dry mouth was reported by 8 participants in the tiotropium group (1.8%) and by 3 placebo-treated participants (0.7%). There were three life-threatening serious adverse events, all in tiotropium-treated participants. Two participants had asthma exacerbations and the third was hospitalised for a cerebral infarction. Cardiac adverse events occurred in <2% of participants and were balanced across the groups. Drug-related cardiac events were reported in two tiotropium-treated participants and one placebo-treated participant.

Considerations for cost impact

In prevalence data from the 2012/13 Quality and Outcomes Framework[9], there are 1,052,147 people in the Midlands and East of England commissioning region registered in GP records as receiving treatment for asthma.

At current prices, the cost of a year's treatment with tiotropium (2.5mcg Respimat MDI, 2 puffs/day) is £408 per patient per year.

References

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8. Kerstjens HA et al. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. *J Allergy Clin Immunol* 2011; 128(2):308-314.
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Launch date: 2002 *Manufacturer: Boehringer Ingelheim*

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