Asthma: tiotropium (Spiriva Respimat)

Evidence summary
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nice.org.uk/guidance/esnm55

Key points from the evidence

The content of this evidence summary was up-to-date in March 2015. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

Two replicate randomised controlled trials (RCTs; total n=912) of identical design evaluated tiotropium (Spiriva Respimat) in adults with poorly controlled asthma and persistent airflow obstruction who were already treated with an inhaled corticosteroid (ICS) and a long-acting beta-2 agonist (LABA). Tiotropium improved peak and trough forced expired volume in 1 second (FEV1) and lengthened the time to first severe exacerbation compared with placebo. Differences between add-on therapy with tiotropium and placebo in patient-assessed asthma control and quality of life were small and did not meet the threshold for the minimal clinically important difference. There are no RCTs comparing tiotropium with other active treatments or in people with asthma without persistent airflow obstruction.

Regulatory status: In September 2014, Spiriva Respimat received a licence extension for asthma.
<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>• After 24 weeks of treatment in 2 RCTs (n=912), tiotropium (Spiriva Respimat) statistically significantly improved peak and trough FEV1 compared with placebo in adults with poorly controlled asthma despite ICS plus LABA therapy.</td>
<td>• The summary of product characteristics states that Spiriva Respimat should be used with caution in people with recent myocardial infarction (within 6 months); any unstable or life-threatening cardiac arrhythmia or cardiac arrhythmia needing intervention or a change in drug therapy in the past year; or hospitalised for heart failure (NYHA class III or IV) within the past year. Dry mouth has been reported as a common adverse effect.</td>
</tr>
<tr>
<td>• In the same RCTs, over 48 weeks tiotropium (Spiriva Respimat) delayed the time to severe asthma exacerbation by 56 days (p=0.03) compared with placebo.</td>
<td>• Spiriva Respimat should not be used as first-line monotherapy for asthma, for the initial treatment of acute episodes of bronchospasm, or for the relief of acute symptoms.</td>
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<tr>
<td></td>
<td>• The efficacy and safety of Spiriva Respimat in children and adolescents has not yet been established.</td>
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<td></td>
<td>• In two 48-week RCTs (n=912), adverse events assessed as drug-related occurred in 5.7% of people who had tiotropium and 4.6% of those who had placebo (in addition to ICS plus LABA therapy).</td>
</tr>
</tbody>
</table>
### Patient factors
- People in the 2 RCTs had asthma with persistent airway obstruction, with FEV1 and FEV1/forced vital capacity (FVC) ratios equivalent to those for people with moderate chronic obstructive pulmonary disease (COPD).
- Tiotropium is only licensed for use in asthma when delivered using the solution for inhalation device, Respimat.
- Tiotropium is taken once-daily.

### Resource implications
- Spiriva Respimat costs £33.50 for 30 days of treatment.
- Increasing from moderate to high dose steroid using an ICS/LABA combination product costs between £5.92 and £38.00 for 30 days.
- Cost of alternative treatments ranges from £2.36 to £17.84.

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**Update**

The following information has become available since this ESNM was produced.

**March 2015: Tiotropium delivered via Respimat compared with Handihaler: no significant difference in mortality in TIOSPIR trial**

The Medicines and Healthcare Products Regulatory Agency has advised that the risk of cardiovascular side effects should be taken into account when prescribing tiotropium delivered via Respimat or Handihaler to patients with certain cardiac conditions, who were excluded from clinical trials of tiotropium (including TIOSPIR). See [Drug Safety Update February 2015](#) for more information.

**Introduction and current guidance**

The [British guideline on the management of asthma](#) (SIGN guideline 141) recommends a stepwise approach for treating asthma, with ICS as the first-choice regular preventer therapy for adults and
children. In adults, if asthma is not adequately controlled using an ICS alone (step 2) the addition of a LABA should be considered (step 3).

If poor control persists despite treatment with moderate dose of ICS and a LABA, treatment options include increasing the dose of ICS (up to 2000 micrograms of beclometasone dipropionate daily) or adding a fourth drug (a leukotriene receptor antagonist, theophylline modified-release or a slow-release beta₂ agonist tablet). The guideline states that there are few clinical trials in this specific patient group to guide management, and recommendations are largely based on extrapolation from trials of add-on therapy to ICS alone.

The British guideline on the management of asthma also states that "long-acting muscarinic antagonists appear to be as effective as salmeterol in the short term and may be superior to doubling the dose of ICS in fixed airways obstruction. Longer term studies are required to confirm this evidence. There would also appear to be benefit in adding tiotropium to ICS and salmeterol in patients who remain symptomatic despite these medications."

Full text of introduction and current guidance.

Product overview

Tiotropium (Spiriva Respimat, Boehringer Ingelheim Limited) is the first long-acting muscarinic antagonist (LAMA) to be licensed for use in asthma. It is licensed as an add-on maintenance bronchodilator treatment in adults with asthma who are currently treated with the maintenance combination of ICS (at least 800 micrograms of budesonide per day or equivalent) and LABA and who experienced 1 or more severe exacerbations in the previous year.

Full text of product overview.

Evidence review

- This evidence summary focuses on 2 replicate RCTs of identical design reported by Kerstjens et al. (2012) that compared tiotropium (delivered using the Respimat device) with placebo in adults whose asthma was poorly controlled despite treatment with an ICS plus a LABA.

- The 2 RCTs included 912 adults (mean age 53 years) with poor asthma control despite treatment with at least 800 micrograms of budesonide or equivalent (median dose 800 micrograms) and a LABA. Participants were required to have an Asthma Control Questionnaire 7 score of 1.5 or higher (suggestive of poor control) and have had at least 1 asthma exacerbation that needed oral corticosteroids in the past year. People with...
diagnosed COPD and people who had recently smoked were excluded from the trials, although participants were required to have persistent airflow obstruction, defined as a post-bronchodilator FEV1 of 80% or less of the predicted value and 70% or less of forced vital capacity (FVC). Participants were randomised to tiotropium 5 micrograms daily (2 puffs delivered using the Respimat device) or placebo.

- The 3 primary end points were peak and trough FEV1 at 24 weeks and the time to first severe exacerbation (deterioration needing initiation or doubling of oral corticosteroids for at least 3 days) measured over 48 weeks.

- At 24 weeks, tiotropium increased peak FEV1 compared with placebo, with a mean difference of 0.086 litres (95% confidence interval [CI] 0.020 to 0.152, *p*=0.01) in trial 1 and 0.154 litres (95% CI 0.091 to 0.217, *p*<0.001) in trial 2. Tiotropium also increased trough FEV1, mean difference compared with placebo of 0.088 litres (95% CI 0.027 to 0.149, *p*=0.01) in trial 1 and 0.111 litres (95%CI 0.053 to 0.169, *p*<0.001) in trial 2. Pooled data from both studies across 48 weeks showed that the time to first severe exacerbation for 25% of each group was increased by 56 days with tiotropium compared with placebo (282 days compared with 226 days, hazard ratio [HR] 0.79, 95% CI 0.62 to 1.00, *p*=0.03). In the tiotropium group, 122 out of 453 people (26.9%) had at least 1 severe exacerbation, compared with 149 out of 454 people (32.8%) in the placebo group (OR 0.75, *p*<0.05).

- Other patient-oriented outcomes were included as secondary end points. Asthma control was assessed using the Asthma Control Questionnaire and quality of life using the Asthma Quality of Life Questionnaire (both patient-assessed questionnaires). The difference between groups was small on both these questionnaires, was only statistically significant in 1 trial, and did not achieve the minimal clinically important differences (0.5 points on both questionnaires) in either trial.

- There are no published RCTs directly comparing tiotropium, used within its licensed indication for asthma, with other active treatments.

- In the two 48-week RCTs (n=912), adverse events attributed to being drug-related were reported in 5.7% of people taking tiotropium and 4.6% of people taking placebo.

Full text of evidence review.

**Context**

Tiotropium (Spiriva Respimat) is licensed for use in adults with poorly controlled asthma who are currently treated with ICS (at least 800 micrograms of budesonide per day or equivalent) and a
LABA. This would place it at step 4 of the British guideline on the management of asthma adult treatment pathway. The British guideline recommends that the following treatment options should be considered at step 4 for adults:

- increase ICS dose up to the equivalent of 2000 micrograms beclometasone dipropionate per day or equivalent
- add a leukotriene receptor antagonist (montelukast or zafirlukast)
- add theophylline modified release
- add a slow-release beta₂ agonist tablet (salbutamol).

Full text of context.

**Estimated impact for the NHS**

People in the 2 RCTs supporting the licence extension for tiotropium in asthma had persistent airway obstruction, with FEV1 and FEV1/FVC ratios similar to those in people with moderate COPD. The benefit of adding tiotropium to existing ICS and LABA in people without persistent airflow obstruction has not been demonstrated in a published RCT.

It is not known how the efficacy of tiotropium as add-on therapy compares with other active treatments recommended at step 4 of the British guideline on the management of asthma.

Tiotropium is only licensed for use in asthma when delivered using the solution for inhalation device, Respimat. Spiriva Respimat should be used with caution in people with recent myocardial infarction within the past 6 months; any unstable or life-threatening cardiac arrhythmia or cardiac arrhythmia needing intervention or a change in drug therapy in the past year; or people who were hospitalised for heart failure (NYHA class III or IV) within the past year. Spiriva Respimat should not be used as first-line monotherapy for asthma or for the initial treatment of acute episodes of bronchospasm, or for the relief of acute symptoms.

The efficacy and safety of Spiriva Respimat in children and adolescents has not yet been established.

Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual patient factors, when making decisions about using tiotropium for treating asthma in adults.
About this evidence summary

‘Evidence summaries: new medicines’ provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

Full evidence summary

Introduction and current guidance

The British guideline on the management of asthma (SIGN guideline 141), published jointly by the Scottish Intercollegiate Guidelines Network and the British Thoracic Society and accredited by NICE, advocates a stepwise approach for treating asthma. Inhaled corticosteroids (ICS) are the first-choice regular preventer therapy for adults and children. If asthma is not adequately controlled using an ICS alone (step 2), add-on therapy may be needed (step 3). For adults and children aged 5 years and over, an ICS and a long-acting beta-2 agonist (LABA) should be considered.

In adults and young people aged over 12 years, if poor control persists after the options at step 3 have been tried, high-dose ICS treatment (up to 2000 micrograms of beclometasone dipropionate or equivalent) or the addition of a fourth drug can be considered (step 4). These additional drugs include leukotriene receptor antagonists, theophylline modified release and slow-release beta2 agonist tablets. The guideline states that there are few clinical trials in this specific patient group to guide management, and recommendations are largely based on extrapolation from trials of add-on therapy to ICS alone.

The British guideline on the management of asthma states that "long-acting muscarinic antagonists appear to be as effective as salmeterol in the short term and may be superior to doubling the dose of ICS in fixed airways obstruction. Longer term studies are required to confirm this evidence. There would also appear to be benefit in adding tiotropium to ICS and salmeterol in patients who remain symptomatic despite these medications." See likely place in therapy section for further details.
Product overview

Drug action

Tiotropium is a long-acting muscarinic antagonist (LAMA). It is available as a powder for inhalation (Spiriva HandiHaler) and as a solution for inhalation (Spiriva Respimat).

Licensed therapeutic indication

Both tiotropium inhalers (Spiriva HandiHaler and Spiriva Respimat, Boehringer Ingelheim Limited) are licensed as maintenance bronchodilator treatment to relieve symptoms of chronic obstructive pulmonary disease (COPD). In September 2014, Spiriva Respimat received a licence extension for use in asthma; this is the first LAMA to be licensed in asthma. It is licensed as an add-on maintenance bronchodilator treatment in adults with asthma who are receiving maintenance treatment with a combination of ICS (at least 800 micrograms of budesonide per day or equivalent) and LABA and who experienced 1 or more severe exacerbations in the previous year.

Course and cost

The recommended dose for adults (for asthma and COPD) is 5 micrograms of tiotropium, given as 2 puffs from the Respimat inhaler once daily, at the same time each day. Each puff contains 2.5 micrograms of tiotropium and is equivalent to 3.124 micrograms of tiotropium bromide monohydrate.

Spiriva Respimat is available as a 60-dose pack, lasting 30 days, at a cost of £33.50 (excluding VAT; costs taken from MIMS, January 2015).

Evidence review

This evidence summary focuses on 2 replicate randomised controlled trials (RCTs) of identical design that provide published evidence for the use of tiotropium in adults whose asthma is poorly controlled despite treatment with an ICS and a LABA (Kerstjens et al. 2012).

Trials 1 and 2 (Kerstjens et al. 2012)

- Design: 2 replicate, randomised, double-blind, placebo-controlled, parallel-group, 48-week trials carried out in 15 countries including the UK.
Population: After a 4-week screening period, 459 participants were randomised in trial 1 and 453 participants were randomised in trial 2. In total, 912 adults aged 18 to 75 years (mean age 53 years) with poor asthma control despite daily therapy with an ICS (at least 800 micrograms of budesonide per day or equivalent [median dose 800 microgram/day]) and a LABA were enrolled. Participants were required to have an Asthma Control Questionnaire 7 (ACQ-7) score of 1.5 or higher (scores on ACQ-7 range between 0 [totally controlled] and 6 [severely uncontrolled], with a minimal clinically important difference of 0.5) and show persistent airflow limitation (defined as a post-bronchodilator forced expired volume in 1 second [FEV1] of 80% or less of the predicted value and 70% or less of forced vital capacity [FVC]). At baseline, participants had a mean ACQ-7 score of 2.6±0.7 and a mean FEV1 of 62.2%±12.7 of the predicted value. Participants were required to have had at least 1 exacerbation that needed oral corticosteroids in the previous 12 months. People with diagnosed COPD and those who had a smoking history of 10 pack-years or more, or who had smoked in the year before the study, were excluded.

Intervention and comparison: Participants were randomised to tiotropium 5 micrograms daily (2 puffs delivered using the Respimat device) or matching placebo. This was add-on therapy to individual pre-trial maintenance therapy consisting of ICS and LABA. Allocation was concealed. Continued use of stable doses of leukotriene receptor antagonists, theophylline modified release, anti-IgE antibody and oral corticosteroids (5 mg or less per day) was permitted. Rescue salbutamol was provided but concurrent use of short-acting antimuscarinic bronchodilators was not allowed during the treatment period.

Outcomes: There were 3 co-primary end points: change from baseline in peak and trough FEV1 at 24 weeks (reported for each trial separately) and time to first severe exacerbation (defined as a deterioration of asthma needing initiation or at least a doubling of oral corticosteroids for at least 3 days) over 48 weeks (based on pooled data from both trials). Secondary end points included patient-assessed asthma control (using ACQ-7), patient-assessed quality of life (using the Asthma Quality of Life Questionnaire [AQLQ], scores range between 1 and 7, with higher scores indicating better quality of life, with a minimal clinically important difference of 0.5) and rescue medication use. Adverse events were also assessed. The efficacy population (n=907) included all randomised participants who received at least 1 dose of a study drug and had at least 1 on-treatment efficacy measurement. The safety population was made up of all randomised participants (n=912).
### Table 1 Summary of trial 1: Kerstjens et al. (2012)

<table>
<thead>
<tr>
<th>Randomised</th>
<th>Tiotropium 5 micrograms daily</th>
<th>Placebo</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=237</td>
<td>0.401 litres (0.025)</td>
<td>0.315 litres (0.026)</td>
<td>Statistically significant increase in peak FEV1 for tiotropium compared with placebo. Mean difference 0.086 litres (95% CI 0.020 to 0.152, p=0.01)</td>
</tr>
<tr>
<td>Co-primary outcome 1:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Change in peak FEV1 at 24 weeks (SE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-primary outcome 2:</td>
<td>0.144 litres (0.024)</td>
<td>0.056 litres (0.025)</td>
<td>Statistically significant increase in trough FEV1 for tiotropium compared with placebo. Mean difference 0.088 litres (95% CI 0.027 to 0.149, p=0.01)</td>
</tr>
<tr>
<td>Change in trough FEV1 at 24 weeks (SE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-primary outcome 3:</td>
<td>Pooled data from trial 1 and trial 2 (n=453) 282 days</td>
<td>Pooled data from trial 1 and trial 2 (n=454) 226 days</td>
<td>Tiotropium statistically significantly increased time to first severe exacerbation by 56 days compared with placebo. Reduction of 21% in relative risk (HR 0.79; 95% CI 0.62 to 1.00, p=0.03)</td>
</tr>
<tr>
<td>Time to first severe exacerbation, up to 48 weeks</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Selected secondary outcomes:

<table>
<thead>
<tr>
<th>Mean ACQ-7 score at 24 weeks (SE)</th>
<th>1.995 (0.051) from baseline of 2.7 (0.7)</th>
<th>2.120 (0.053) from baseline of 2.7 (0.7)</th>
<th>No statistically significant difference in score between groups. Mean difference −0.126 (95% CI −0.256 to 0.005, p=0.06)</th>
</tr>
</thead>
</table>
Mean AQLQ total score at week 24 (SE)b,e

<table>
<thead>
<tr>
<th></th>
<th>Mean Score (SE)</th>
<th>Baseline Score (SE)</th>
<th>Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiotropium</td>
<td>5.125 (0.057)</td>
<td>4.6 (1.1)</td>
<td>-0.042 (-0.103 to 0.186)</td>
<td>0.57</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.084 (0.059)</td>
<td>4.6 (1.1)</td>
<td>-0.042 (-0.130 to 0.046)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

No statistically significant difference in score between groups.

Mean change in weekly rescue medication use from baseline to 24 weeks, puffs per day (SE)b

<table>
<thead>
<tr>
<th></th>
<th>Mean Change (SE)</th>
<th>Baseline Change (SE)</th>
<th>Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiotropium</td>
<td>-0.806 (0.135)</td>
<td>-0.714 (0.140)</td>
<td>-0.092 (-0.430 to 0.246)</td>
<td>0.59</td>
</tr>
<tr>
<td>Placebo</td>
<td>-0.714 (0.140)</td>
<td>-0.714 (0.140)</td>
<td>-0.000 (-0.430 to 0.246)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

No statistically significant difference between tiotropium and placebo in rescue medication use.

Safetyf

<table>
<thead>
<tr>
<th></th>
<th>Tiotropium</th>
<th>Placebo</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of people reporting serious adverse events</td>
<td>18/237 (7.6%)</td>
<td>15/222 (6.8%)</td>
<td>237</td>
</tr>
</tbody>
</table>

No statistical analysis reported.

Abbreviations: ACQ-7, Asthma Control Questionnaire 7; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; FEV1, forced expired volume in 1 second; HR, hazard ratio; SE, standard error.

a Efficacy population includes all randomised participants who received at least 1 dose of a study drug and had at least 1 on-treatment efficacy measurement.
b Additional trial results taken from clinicaltrials.gov NCT00772538.
c Representing the time until at least 25% of the participants (first quartile) had a first severe exacerbation.
d ACQ-7: Asthma Control Questionnaire 7 – a measure of asthma control, scores range between 0 (totally controlled) and 6 (severely uncontrolled), with a minimal clinically important difference of 0.5.
e AQLQ: Asthma Quality of Life Questionnaire – a measure of quality of life, scores range between 1 and 7, higher scores indicating better quality of life, with a minimal clinically important difference of 0.5.
f Safety population includes all randomised participants.

Table 2 Summary of trial 2: Kerstjens et al. (2012)
<table>
<thead>
<tr>
<th>Efficacy&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Randomised</th>
<th>n=219</th>
<th>n=234</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-primary outcome:</td>
<td>n=216&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n=232&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Change in peak FEV1</td>
<td>0.401 litres (0.025)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.248 litres (0.024)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Statistically significant increase in peak FEV1 for tiotropium compared with placebo. Mean difference 0.154 L (95% CI 0.091 to 0.217, p&lt;0.001)</td>
</tr>
<tr>
<td>Change in trough FEV1</td>
<td>0.155 litres (0.023)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.044 litres (0.022)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Statistically significant increase in trough FEV1 for tiotropium compared with placebo. Mean difference 0.111 L (95% CI 0.053 to 0.169, p&lt;0.001)</td>
</tr>
<tr>
<td>Co-primary outcome:</td>
<td>Pooled data from trial 1 and trial 2 (n=453) 282 days</td>
<td>Pooled data from trial 1 and trial 2 (n=454) 226 days</td>
<td>Tiotropium statistically significantly increased time to first severe exacerbation by 56 days compared with placebo. Reduction of 21% in relative risk (HR 0.79; 95% CI 0.62 to 1.00, p=0.03)</td>
</tr>
</tbody>
</table>

**Selected secondary outcomes:**

| Mean ACQ-7 score at 24 weeks (SE)<sup>b,d</sup> | 2.011 (0.052) from baseline of 2.6 (0.7) | 2.210 (0.050) from baseline of 2.6 (0.7) | Tiotropium statistically significantly improved mean asthma control score compared with placebo. Mean difference −0.199 (−0.330 to −0.068, p=0.003)<sup>b</sup> |
| Mean AQLQ total score at 24 weeks (SE)<sup>b,e</sup> | 5.047 (0.061) from baseline of 4.6 (1.0) | 4.869 (0.058) from baseline of 4.7 (1.1) | Tiotropium statistically significantly improved mean quality of life score compared with placebo. Mean difference 0.178 (95% CI 0.025 to 0.331, p=0.02<sup>b</sup>) |
Mean change in weekly rescue medication use from baseline to 24 weeks, puffs per day (SE)

|          | −1.144 (0.163) | −0.881 (0.158) | No statistically significant difference between tiotropium and placebo in rescue medication use. Mean difference −0.263 (95% CI −0.635 to 0.110, p=0.17) |

Safety

|          | n=219          | n=234          | No statistical analysis reported. |

Number of people reporting serious adverse events

|          | 19/219 (8.7%)  | 25/234 (10.7%) | |

Abbreviations: ACQ-7, Asthma Control Questionnaire 7; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; FEV1, forced expired volume in 1 second; HR, hazard ratio; SE, standard error.

a Efficacy population includes all randomised participants who received at least 1 dose of a study drug and had at least 1 on-treatment efficacy measurement.
b Additional trial results taken from clinicaltrials.gov NCT00776984.
c Representing the time until at least 25% of the participants (first quartile) had a first severe exacerbation.
d ACQ-7: Asthma Control Questionnaire 7 – a measure of asthma control, scores range between 0 (totally controlled) and 6 (severely uncontrolled), with a minimal clinically important difference of 0.5.
e AQLQ: Asthma Quality of Life Questionnaire – a measure of quality of life, scores range between 1 and 7, higher scores indicating better quality of life, with a minimal clinically important difference of 0.5.
f Safety population includes all randomised participants.

Clinical effectiveness

Tiotropium compared with placebo

Pooled results given in the summary of product characteristics from 907 participants in trial 1 and trial 2 in Kerstjens et al. (2012) showed that over 24 weeks, tiotropium improved peak and trough FEV1 (co-primary outcomes) by 0.110 litres (95% CI 0.063 to 0.158, p<0.0001) and 0.093 litres (95% CI 0.050 to 0.137, p<0.0001) respectively in people with poor asthma control despite daily therapy with an ICS and a LABA (median ICS dose 800 micrograms per day of budesonide or equivalent). The time to first severe exacerbation in 25% of the participants (third co-primary
outcome) was increased by 56 days with tiotropium compared with placebo (282 days compared with 226 days; hazard ratio [HR] 0.79, 95% CI 0.62 to 1.00, p=0.03).

Add-on therapy with tiotropium produced statistically significant improvements for most of the lung function secondary outcomes compared with placebo.

Asthma control was assessed using the Asthma Control Questionnaire 7 (ACQ-7) and quality of life using the Asthma Quality of Life Questionnaire (AQLQ). Tiotropium improved the ACQ-7 score from baseline to week 24 by 0.71 in trial 1 and 0.59 in trial 2, with placebo improving the ACQ-7 score by 0.39 and 0.58 in trial 1 and 2, respectively. The AQLQ score improved in the tiotropium group by 0.45 and 0.53 in trials 1 and 2, respectively; in the placebo group scores improved by 0.17 and 0.48, respectively, from baseline to week 24. The difference between groups was small on both these questionnaires; it was only statistically significant in trial 2 and did not achieve the minimal clinically important differences (0.5 points on both questionnaires) in either trial.

**Tiotropium compared with other active treatments**

There are no published RCTs directly comparing tiotropium with other active treatments, when tiotropium is used within its licensed indication for asthma (as add-on therapy to ICS and LABA).

A double-blind, randomised, placebo-controlled, crossover study (Fardon et al. 2007) showed that adding salmeterol plus tiotropium after a reduction in ICS dose (fluticasone propionate) improved lung function compared with adding salmeterol plus placebo. However, the trial involved few participants (n=18), was short term (each treatment arm lasted 4 weeks) and had disease-oriented rather than patient-oriented outcomes. In addition, tiotropium was given using the HandiHaler device, which is not licensed for use in asthma.

Peters et al. (2010) reported a 3-way, double-blind, triple-dummy crossover trial (n=210) which compared the addition of tiotropium to doubling the dose of ICS or the addition of a LABA (salmeterol) in people whose asthma was poorly controlled with ICS alone. The trial showed that, for lung function, adding tiotropium was superior to doubling the ICS dose and non-inferior to adding salmeterol to an ICS. However, caution should be used when considering these results because tiotropium was not used in line with its licence for treating asthma (as add-on therapy to an ICS and a LABA). The trial was short term (each treatment arm lasted 14 weeks), had a disease-oriented primary outcome and used the HandiHaler device, which is not licensed for use in asthma.

A 16-week, double-blind, double-dummy RCT (Bateman et al. 2011) compared tiotropium (delivered using the Respimat device), salmeterol and placebo as add-on therapy to ICS in people...
with asthma and the B16-Arg/Arg genotype (n=388). Tiotropium was superior to placebo and non-inferior to salmeterol in maintaining improved lung function. However, the use of tiotropium in this study was outside its licence for treating asthma.

Safety and tolerability

In the 2 replicate 48-week RCTs of identical design (Kerstjens et al. 2012), adverse events were reported in 335 out of 456 people (73.5%) taking tiotropium and 366 out of 456 people (80.3%) taking placebo. Adverse events were assessed as being drug related in 26 people (5.7%) taking tiotropium and 21 people (4.6%) taking placebo. No statistical analysis was reported for either measure.

Serious adverse events were reported in 37 people (8.1%) taking tiotropium and 40 people (8.8%) taking placebo (no statistical analysis reported). Three of the serious adverse events (2 asthma exacerbations and 1 cerebral infarction) were considered life threatening; all occurred in the tiotropium group. No deaths occurred.

An MHRA Drug Safety Update from November 2010 advised that Spiriva Respimat was associated with a non-significant increase in all-cause mortality compared with placebo. The summary of product characteristics states that Spiriva Respimat should be used with caution in people with recent myocardial infarction within the past 6 months; any unstable or life-threatening cardiac arrhythmia or cardiac arrhythmia needing intervention or a change in drug therapy in the past year; or people who were hospitalised for heart failure (NYHA class III or IV) within the past year. The recommended dose should not be exceeded. Kerstjens et al. (2012) reported that in trial 1 there were 5 serious cardiac adverse events (arrhythmia supraventricular, atrial fibrillation, coronary artery occlusion, coronary artery stenosis and ventricular tachycardia) in the tiotropium group. No serious cardiac adverse events were reported in the placebo group in trial 1, or in either group in trial 2.

The summary of product characteristics for Spiriva Respimat states that it should not be used as (first-line) monotherapy for asthma, or for the initial treatment of acute episodes of bronchospasm, or for the relief of acute symptoms. The efficacy and safety of Spiriva Respimat in children and adolescents has not yet been established. People with asthma should be advised to continue taking anti-inflammatory therapy with ICS unchanged after the introduction of Spiriva Respimat, even if their symptoms improve.

Consistent with its anticholinergic activity, tiotropium should be used with caution in people with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction. Dry mouth has been
reported as a common adverse effect with tiotropium (occurring in between 1 in 10 and 1 in 100 people). See the summary of product characteristics for more information.

Evidence strengths and limitations

Evidence to support the use of tiotropium in people with asthma that is poorly controlled despite treatment with an ICS and a LABA comes from 2 replicate double-blind RCTs of identical design (n=912), the results of which are reported by Kerstjens et al. (2012). The allocation method described suggests that allocation was concealed. The authors note that the baseline characteristics were similar in the 2 trials and well-balanced between the study groups.

Two of the co-primary outcomes measures of these studies were peak and trough FEV1, both disease-oriented outcomes. However, time to first severe exacerbation, the third co-primary outcome, is patient oriented, as were a number of secondary outcomes measured in these trials.

Although people with a past diagnosis of COPD were excluded from the study, a post-bronchodilator FEV1/FVC ratio of 0.7 or less and FEV1 of 80% or less was an inclusion criterion, meaning participants had the same persistent airflow obstruction as people with moderate, stage 2 COPD (NICE guideline on management of chronic obstructive pulmonary disease). The benefit of adding tiotropium to existing ICS and LABA in people without persistent airflow obstruction has not been demonstrated in a published RCT.

The 2 trials supporting the licence extension for asthma were placebo controlled. There are no active comparator studies in people with asthma that is poorly controlled despite treatment with an ICS and a LABA.

Context

Alternative treatments

Tiotropium (Spiriva Respimat) is licensed for adults with poorly controlled asthma who are currently treated with ICS (at least 800 micrograms of budesonide per day or equivalent) and a LABA. This would place it at step 4 of the treatment pathway for adults in the British guideline on the management of asthma. The British guideline recommends the following treatment options at step 4 for adults:

- increase ICS dose up to the equivalent of 2000 micrograms of beclometasone dipropionate per day
- add a leukotriene receptor antagonist (montelukast or zafirlukast)
- add theophylline modified release
- add a slow-release beta<sub>2</sub> agonist tablet (salbutamol).

### Table 3 Costs of alternative treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose in adults&lt;sup&gt;a&lt;/sup&gt;</th>
<th>30-day cost excluding VAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiotropium 2.5 micrograms (Spiriva Respimat)</td>
<td>2 inhalations once a day</td>
<td>£33.50&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fluticasone propionate/ salmeterol 500/50 micrograms (Seretide Accuhaler)</td>
<td>Maximum daily dose 1 inhalation twice a day</td>
<td>£40.92&lt;sup&gt;b&lt;/sup&gt; (60-dose unit) Cost of increasing from moderate to high dose steroid=£5.92&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fluticasone propionate/ salmeterol 250/25 micrograms (Seretide Evohaler)</td>
<td>Maximum daily dose 2 inhalations twice a day</td>
<td>£59.48&lt;sup&gt;b&lt;/sup&gt; (120-dose unit) Cost of increasing from moderate to high dose steroid=£24.48&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fluticasone propionate/ formoterol 250/10 micrograms (Flutiform)</td>
<td>Maximum daily dose 2 inhalations twice a day</td>
<td>£45.56&lt;sup&gt;b&lt;/sup&gt; (120-dose unit) Cost of increasing from moderate to high dose steroid=£16.30&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Budesonide/formoterol 400/12 micrograms (Symbicort Turbohaler)</td>
<td>Maximum daily dose 2 inhalations twice a day</td>
<td>£76.00&lt;sup&gt;b&lt;/sup&gt; (2×60-dose unit) Cost of increasing from moderate to high dose steroid=£38.00&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Budesonide/formoterol 320/9 micrograms (DuoResp Spiromax)</td>
<td>Maximum daily dose 2 inhalations twice a day</td>
<td>£59.94&lt;sup&gt;c&lt;/sup&gt; (2x60-dose unit) Cost of increasing from moderate to high dose steroid= £29.97&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fluticasone furoate/ vilanterol 184/22 micrograms (Relvar Ellipta)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Maximum daily dose 1 inhalation once a day</td>
<td>£38.87&lt;sup&gt;c&lt;/sup&gt; (30-dose unit) Cost of increasing from moderate to high dose steroid= £11.07&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Usual Dose</td>
<td>Cost</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------------------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Montelukast tablets</td>
<td>Usual dose 10 mg once a day</td>
<td>£2.36&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Zafirlukast tablets</td>
<td>Usual dose 20 mg twice a day</td>
<td>£19.02&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Theophylline modified-release</td>
<td>Usual dose 175 mg to 500 mg twice a day (dose dependent on brand)</td>
<td>£3.17 to £17.84&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Theophylline modified-release</td>
<td>Usual dose 8 mg twice a day</td>
<td>£10.38&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Terbutaline tablets</td>
<td>Usual dose 5 mg 3 times a day</td>
<td>£4.42&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Doses do not represent the full range that can be used. Taken from the relevant summaries of product characteristics.

<sup>b</sup> Costs based on the Drug Tariff, January 2015; excluding VAT.

<sup>c</sup> Costs based on MIMS, January 2015; excluding VAT.

<sup>d</sup> Represents a change from Seretide 250 Accuhaler to Seretide 500 Accuhaler (1 inhalation twice a day).

<sup>e</sup> Represents a change from Seretide 125 Evohaler to Seretide 250 Evohaler (2 inhalations twice a day).

<sup>f</sup> Represents a change from Flutiform 125/5 to Flutiform 250/10 (2 inhalations twice a day).

<sup>g</sup> Represents a change from Symbicort Turbohaler 400/12, 2 inhalations twice a day to 1 inhalation twice a day.

<sup>h</sup> Represents a change from DuoResp Spiromax 320/9, 2 inhalations twice a day to 1 inhalation twice a day.

<sup>i</sup> Relvar Ellipta contains fluticasone furoate. Fluticasone furoate 92 micrograms once a day is approximately equivalent to fluticasone propionate 250 micrograms twice a day. The British guideline on the management of asthma indicates that 250 micrograms fluticasone propionate twice a day is approximately equivalent to 1000 micrograms beclometasone dipropionate per day.

<sup>j</sup> Represents a change from Relvar Ellipta 92/22 to Relvar Ellipta 184/22 (1 inhalation once a day).
Estimated impact for the NHS

Likely place in therapy

The British guideline on the management of asthma (SIGN guideline 141) recommends for people whose asthma is not adequately controlled on moderate dose ICS plus LABA therapy (step 3), either increasing the dose of ICS up to 2000 micrograms of beclometasone dipropionate per day or equivalent or the addition of a fourth drug (a leukotriene receptor antagonist, theophylline modified release or a slow-release beta2 agonist tablet; step 4). The guideline states that there are few clinical trials in this specific patient group to guide management, and recommendations are largely based on extrapolation from trials of add-on therapy to ICS alone. There are no controlled trials indicating the best option, although the potential for side effects is greater with theophyllines and slow-release beta2 agonist tablets. If a trial of an add-on treatment is ineffective, the British guideline recommends stopping the drug (or in the case of increased dose of ICS, reducing to the original dose).

The guideline also states that long-acting muscarinic antagonists appear to be as effective as salmeterol in the short term and may be superior to doubling the dose of ICS in fixed airway obstruction, but longer-term studies are needed to confirm this. The guideline states that there also appears to be benefit in adding tiotropium to ICS and salmeterol in people who remain symptomatic despite these medications.

In Kerstjens et al. (2012), tiotropium compared with placebo statistically significantly improved lung function (peak and trough FEV1) and delayed the time to first severe asthma exacerbation in adults with poorly controlled asthma despite treatment with ICS plus LABA. However, differences between add-on therapy with tiotropium and placebo in patient-assessed asthma control and quality of life were small and did not meet the threshold for the minimal clinically important difference.

There are no published studies comparing tiotropium (as add-on therapy to ICS and LABA) with other active treatments recommended at step 4 of the British Asthma guideline. In addition, people recruited to the 2 trials reported by Kerstjens et al. (2012) had asthma with persistent airway obstruction, with FEV1 and FEV/FVC ratios the same as for people with moderate COPD.

In Kerstjens et al. (2012), tiotropium was given using the Respimat device, which is the licensed product. The summary of product characteristics for Spiriva Respimat states that it should be used with caution in people with recent myocardial infarction; any unstable or life-threatening cardiac
arrhythmia or cardiac arrhythmia needing intervention or a change in drug therapy in the past year; or people who were hospitalised for heart failure (NYHA class III or IV) within the past year.

Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual patient factors, when making decisions about using tiotropium for treating asthma in adults.

**Estimated usage**

Using data from the NHS Quality and Outcomes Framework, the manufacturer estimates that in England 4738 people per 100,000 population are adults with asthma. Based on data from Kerstjens et al. (2012), the manufacturer predicts that in England 763 people per 100,000 population will be eligible for treatment with tiotropium. It estimates that uptake will be 8 per 100,000 population (approximately 4312 people in England) in the first year, increasing to 84 per 100,000 (approximately 45,276 people) in year 5 (Boehringer Ingelheim: personal communication, November 2014).

**Relevance to NICE guidance programmes**

Tiotropium for asthma was not considered appropriate for a NICE technology appraisal and is not currently planned into any other NICE work programme.

**References**

Bateman ED, Kornmann O, Schmidt P et al. (2011) Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. *Journal of Allergy and Clinical Immunology* 128: 315–22

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US National Institutes of Health (2014) ClinicalTrials.gov Identifier: NCT00772538 [online; accessed 1 December 2014]


Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Dr Capstick has received payment for educational events from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer, and Teva.

Dr Green has received speakers fees in the past 5 years from GlaxoSmithKline, Chiesi, Novartis and conference travel sponsorship in the last 5 years from Novartis and Almirall.

Dr Singh had no relevant interests to declare.

Changes after publication

March 2015: Minor maintenance
About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

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