New Medicine Assessment

Tiotropium 2.5 micrograms (Spiriva® Respimat®▼)

Asthma in adults

Recommendation: Amber 0

Tiotropium 2.5 micrograms (Spiriva® Respimat®▼) is recommended as add-on maintenance bronchodilator treatment in adult patients with asthma who meet **all** of the following criteria:

- persistent airflow limitation demonstrated by a FEV_1 <80% predicted and a ratio of FEV_1/FVC <70% **and**
- currently treated with the maintenance combination of inhaled corticosteroids (≥ 800 micrograms budesonide/day or equivalent*) and long-acting β_2 agonists **and**
- experienced one or more severe exacerbations in the previous year.

Summary of supporting evidence:

- Tiotropium was compared against placebo as add-on therapy to high dose ICS and LABA in two, replicate, 48-week, randomised, phase 3 trials, in asthma patients with persistent airflow limitations, who had experience of at least one severe exacerbation in the last year.
- The changes from baseline in the co-primary endpoints of peak and trough FEV_1 were statistically significantly greater with tiotropium than those achieved with placebo at 24 weeks; however, the improvements over placebo were smaller than those normally considered to be clinically meaningful in asthma patients with baseline airways obstruction (e.g. 12% or 200mL). There were no statistically significant improvements over placebo for secondary endpoints of the number of asthma symptom-free days or the use of rescue medication, and no clinically meaningful improvement in asthma symptom control or patient quality of life as assessed by patients in validated questionnaires.
- Tiotropium significantly increased the co-primary endpoint of time to first severe asthma exacerbation (defined as asthma deterioration needing initiation or doubling of systemic corticosteroids), and also significantly reduced the proportion of patients experiencing a severe exacerbation and the number of severe exacerbations per patient year. In post hoc analysis, 15 patients needed to be treated with tiotropium for a year to avoid one severe exacerbation. Tiotropium did not significantly reduce asthma-related hospitalisations.
- The trials excluded patients with COPD, but all patients enrolled in the trials were required to have FEV_1 ≤80% predicted and a ratio of FEV_1/FVC ≤70%, which would place them in the same category of persistent airflow limitation as patients with COPD. The results may therefore not be generalisable to all patients with uncontrolled asthma who are receiving

ICS plus LABA maintenance treatment.

- Trial data to support the use of other add-on treatments at Step 4 of the BTS/SIGN guideline is generally lacking. In addition, higher dose ICS, theophyllines and oral β_2 agonists have well-documented side effects and/or drug interactions.
- A published cost effectiveness analysis of tiotropium compared against no other active treatment, based on the above trials, estimated an incremental cost per quality-adjusted life year gained of around £22,000. This analysis assumed a constant stable benefit for tiotropium over a lifetime horizon. Tiotropium had a 45% probability of having an incremental cost per QALY gained below the usual threshold range for cost effectiveness (£20-30,000 per QALY gained) and a 34% probability that it exceeded this range.
- There are no precise data on the prevalence of asthma requiring treatment at Step 4 of the BTS/SIGN guidelines. Based QOF asthma registry data, 79% of asthma patients being adults and assuming 5-10% of patients may have difficult to treat asthma, there may be as many as 4,084 – 8,168 adults with asthma potentially eligible for treatment with tiotropium in Lancashire. Likely uptake is unknown however based on an acquisition cost of £408 per patient per year and 10% to 50% of eligible patients receiving tiotropium; the potential cost pressure of Lancashire is £164,167 - £1,640,000.

*Approximately equivalent to becolmetasone dipropionate 800 microgram/day

Details of Review

Name of medicine (generic & brand name)**:**

Tiotropium 2.5 micrograms (Spiriva® Respimat®) solution for inhalation [Boehringer Ingelheim]

Strength(s) and form(s):

Tiotropium 2.5 micrograms solution for inhalation

Dose and administration:

5.0 microgram tiotropium given as two puffs from the Respimat® inhaler once daily, at the same time of the day

BNF therapeutic class / mode of action

3.1 Bronchodilators / 3.1.2 Antimuscarinic bronchodilators

Licensed indication(s):

Add-on maintenance bronchodilator treatment in adult patients with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (≥800 µg budesonide/day or equivalent) and long-acting β_2 agonists and who experienced one or more severe exacerbations in the previous year.

Proposed use (if different from, or in addition to, licensed indication above):

As licensed indication.

Course and cost:

30 days' treatment = £33.50; annual cost = £408

Mims online accessed 21/11/14

Current standard of care/comparator therapies:

Options beyond step 3 of the BTS/SIGN guideline include increasing inhaled corticosteroid dose to 2000 micrograms beclometasone dipropionate equivalent per day, or addition of a 4th agent: leukotriene receptor antagonist, theophylline, oral slow-release β_2 agonist (but caution in those on long-acting β_2 agonists)

Relevant national guidance:

BTS/SIGN Clinical guideline 141. British guideline on the management of asthma; October 2014

Background and context

Asthma is a chronic inflammatory condition of the airways. The cause is not certain but involves hyper-responsiveness to a range of stimuli, leading to narrowing of the airways and symptoms of breathlessness, tightness in the chest, coughing and wheezing. The narrowing of the airways is usually reversible, leading to intermittent symptoms; however, severity and response to treatment can vary markedly. In some people, the chronic inflammation can lead to irreversible airflow obstruction, complicating diagnosis and potentially impacting on response to treatment [1,2].

The goal of asthma management is for people to be free from symptoms and able to lead a normal, active life [3]. In addition to avoidance of known stimuli and a range of potential non-pharmacological approaches, the BTS/SIGN asthma guideline, updated in October 2014, recommends a stepwise approach to pharmacological treatment with the aim of abolishing symptoms as soon as possible and maintaining control. Patients should start treatment at the step most appropriate to the initial severity of their asthma, and step up and down based on their response and control achieved. Adherence and inhaler technique should be assessed before adding new therapies [2].

The BTS/SIGN guidelines should be consulted for full details [2], but in brief:

Step 1: patients with mild intermittent asthma symptoms should receive reliever therapy as an inhaled short-acting β2 agonist (SABA) for use as required.

Step 2: in patients who have experienced asthma attacks in the last two years, or are symptomatic or using their reliever three times per week or more, or experience night time waking once a week or more, treatment with regular inhaled corticosteroid (ICS) as a preventative therapy is recommended, with titration of the dose to the lowest at which effective control is maintained.

Step 3: in those not achieving control, add-on treatment is recommended, with the first choice in adults being a long-acting β_2 agonist (LABA). If a response to LABA is achieved but control remains sub-optimal, an increase in the dose of ICS (up to 800 micrograms/day beclometasone dipropionate [BDP] equivalent.

Step 4: in the small proportion of patients who still have poor control on moderate doses of ICS in combination with a LABA, there are few clinical trials to guide management. Options include increasing the ICS dose up to 2,000 micrograms BPD equivalent in adults, or adding in a leukotriene receptor antagonist (LTRA), or theophylline, or oral slow-release β_2 agonist tablets (although caution is needed in those already using LABA). Trial evidence to guide management of patients at this Step is lacking. Although not included as a recommendation, the guideline notes that there would appear to be benefit in adding tiotropium to ICS and salmeterol in patients who remain symptomatic despite these medications.

Step 5: in patients with very severe asthma who still remain uncontrolled, continuous or frequent use of oral corticosteroid tablets is required. Referral to specialist care is recommended before proceeding to this step.

Tiotropium 2.5 micrograms solution for inhalation (Spiriva® Respimat®) has recently received a marketing authorisation for use as add-on maintenance bronchodilator treatment in adult patients

with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (≥800 micrograms budesonide/day or equivalent*) and long-acting β_2 agonists and who experienced one or more severe exacerbations in the previous year [4]. These patients would appear to be broadly equivalent to those at Step 4 of the BTS/SIGN treatment pathway [2]. The license relates to use in adults only and does not extend to the tiotropium 18 micrograms inhalation powder formulation delivered by the HandiHaler® device.

*Approximately equivalent to becolmetasone dipropionate 800 microgram/day

Summary of evidence

Summary of efficacy data in proposed use:

There are no trials directly comparing tiotropium in its licensed indication for asthma against alternative active agents.

Key efficacy data relevant to the licensed indication are available from two replicate, phase III, 48-week, double-blind, randomised, placebo-controlled trials. These assessed the addition of tiotropium 5.0 micrograms (as 2 x 2.5 microgram doses) via the Respimat® device in adults with symptomatic asthma despite treatment with high-dose inhaled ICS (≥800 micrograms budesonide/day or equivalent*) plus LABA [5], i.e. patients who were broadly equivalent to those at Step 4 of the BTS/SIGN treatment pathway [2]. Patients were required to have had at least one severe asthma exacerbation (defined as deterioration of asthma necessitating initiation or at least a doubling of systemic glucocorticoids for >3 days) in the previous year, and had persistent airflow obstruction (Table 1, page 14-16).

Three pre-specified co-primary endpoints were assessed: peak FEV_1 in the first 3 hours after dosing and trough FEV_1 were assessed at 24 weeks in each trial separately, and time to first severe exacerbation (defined as above) was assessed at 48 weeks using pooled data from the two trials. The change from baseline in peak FEV_1 was statistically significantly greater with tiotropium compared with placebo in both trials (difference 86mL [95%CI: 20 to 152; p<0.05] in trial 1, 154mL [95%CI: 91 to 217; p<0.001] in trial 2), as was the change from baseline in trough FEV1 (difference 88mL [95%CI: 27 to 149; p<0.01] in trial 1, 111mL [95%CI: 53 to 169; p<0.001] in trial 2). Time to first severe exacerbation was also statistically significantly improved for tiotropium vs. placebo at 48 weeks (282 days vs. 226 days; hazard ratio 0.79 [95%CI: 0.62 to 1.00]; p=0.03]) [5].

In secondary and exploratory analyses, the statistically significant improvements in peak FEV_1 were maintained at 48 weeks in both trials; however, trough FEV_1 was no longer statistically significantly in favour of tiotropium in trial 1. The proportion of patients experiencing one or more episodes of asthma worsening (49.9% vs. 63.2%, p<0.001) or severe exacerbations (26.9% vs. 32.8%; p<0.05), and the number of severe exacerbations per patient-year (0.530 vs. 0.663; p=0.046) significantly favoured tiotropium over placebo. In a post hoc analysis, the number needed to treat (NNT) to prevent one severe exacerbation during the 48 week treatment period was reported to be 15. However, there was no significant difference in the proportion of patients experiencing one or more asthma hospitalisations. Based on available data up to 24 weeks, there were no significant differences in the number of asthma symptom-free days or use of rescue

medication, and no clinically meaningful differences in overall asthma control and health-related quality of life measured using validated patient-completed questionnaires [5].

Other efficacy data:

Several systematic literature reviews of tiotropium have been published and generally conclude it improves lung function in patients with persistent asthma, and reduces severe exacerbations [6-10]. However, these reviews have included the two key trials discussed above alongside several other trials that have been conducted in patient groups that do not meet the licensed indication, and in some cases using tiotropium 18 micrograms via the HandiHaler® device, which is not licensed for use in asthma patients in the UK.

The BTS/SIGN guideline notes there are very few clinical trials to guide management at Step 4; the recommendations at this step are based largely on extrapolation of trials of add-on therapy to ICS alone [2]. It is therefore difficult to formulate a measure of the efficacy of tiotropium relative to alternative agents that are recommended as possible add-on therapies at Step 4, particularly as up to 20% of patients were taking these alternative agents in addition to ICS and LABA when randomised into the key tiotropium trials (Table 1) [5].

Summary of safety data:

Adverse events reported in the trials of tiotropium in the treatment of asthma were generally compatible with the known adverse events of its use in COPD [4].

Across both of the key asthma trials, serious adverse events occurred in 8.1% on tiotropium and 8.8% on placebo, while adverse events of any severity occurred in 73.5% and 80.3%, respectively [5]. Among the adverse events reported by at least 2% of patients the only adverse effect to occur significantly more commonly with tiotropium than placebo was allergic rhinitis (2.9% vs. 0.7%). Dry mouth was reported by 1.8% on tiotropium compared with 0.7% on placebo. Cardiac adverse events occurred in less than 2% of patients and were well balanced between the study groups. Drug-related cardiac events were reported in two patients (0.4%) in the tiotropium group and one patient (0.2%) in the placebo group. The SPC recommends caution in the use of tiotropium in patients with known cardiac rhythm disorders [4], and the key trials excluded patients with history of cardiovascular disease [5].

Alternative approaches at Step 4 of the BTS/SIGN guideline include further increasing the dose of ICS, or use of other add-on treatments such as theophylline or oral β_2 agonist tablets, which have well-documented adverse effects and drug interactions [2].

Strengths and limitations of the evidence:

Overall study design:

- The two key studies were sufficiently long to demonstrate effects on lung function and symptoms (24 weeks), and on exacerbations (48 weeks) [5]. The use of lung function measures and exacerbations as co-primary endpoints follows the current recommendations of the EMA for the design of trials of bronchodilators added on to ICS in asthma [11].
- The trials appear to have good internal validity and to be of relatively low risk of bias based on their design (Table 1).

Population:

- Patients enrolled in the trials reflect the licensed indication well, and broadly reflect patients at Step 4 of the BTS/SIGN asthma guideline. Patients with a history of cardiovascular disease were excluded.
- The trials aimed to exclude patients with COPD, but all patients enrolled in the trials were required to have FEV_1 ≤80% predicted and a ratio of FEV_1/FVC ≤70%, which would place them in the same category of persistent airflow limitation as patients with COPD [12]. The treatment effect in patients without the same degree of persistent airflow limitation are unknown, results may therefore not be generalisable to all patients with uncontrolled asthma who are receiving ICS plus LABA maintenance treatment.

Intervention:

- Patients in the trials received the licensed formulation and dose of tiotropium.
- Patients were responsible for providing their own ICS and LABA maintenance treatment in the trial and up to a fifth of patients were already using other add-on agents to their ICS and LABA maintenance treatment [5]. Although adherence with tiotropium and placebo treatment was checked, it is unclear how adherent patients were with their maintenance treatments, which could influence their capacity to benefit from add-on bronchodilator therapy with tiotropium [12]. BTS/SIGN guidelines emphasise the importance of checking adherence and inhaler technique before adding new therapies [2].

Comparator:

- The relevant tiotropium trials used placebo as the comparator, which provides little evidence to determine the efficacy of tiotropium relative to other agents used as add-on treatments in patients at Step 4 of the BTS/SIGN guideline (e.g. theophylline, LTRAs).
- Although the tiotropium trials were placebo-controlled, tiotropium has been assessed in two large, phase 3 trials, conducted specifically in this patient group [5]. In contrast, other agents currently recommended as add-on treatment options at Step 4 of the BTS/SIGN guideline are not supported by robust trial evidence specific to this use [2].

Outcomes:

- The changes from baseline in peak and trough FEV_1 were statistically significantly greater with tiotropium than those achieved with placebo at 24 weeks; however, the improvements

over placebo were small in both trials (peak FEV_1 86 and 154mL, trough FEV_1 88 and 111mL, or <10%), and a significant benefit in trough FEV_1 was no longer observed at 48 weeks in one of the trials. American Thoracic Society/European Respiratory Society recommendations for asthma trial endpoints suggest an improvement in FEV_1 $\geq$12% and 200mL in patients with asthma with baseline airway obstruction is usually considered to be significant, and the minimal important difference based on patient perception of change, is about 10% [13].

- Time to first severe asthma exacerbation was significantly greater with tiotropium, based on at least 25% of patients experiencing severe exacerbation. The proportion of patients experiencing a severe exacerbation and the number of severe exacerbations per patient year were also statistically significantly improved with tiotropium at 48 weeks. Severe exacerbation was defined as asthma deterioration needing initiation or doubling of systemic corticosteroids. Tiotropium did not significantly reduce hospitalisation for asthma symptoms.
- The statistically significant improvements in FEV_1 and time to first severe exacerbation with tiotropium did not translate into clinically meaningful differences in patients' perceptions of asthma control and quality of life measured by validated questionnaires, or reduce the number of asthma symptom free days or use of rescue medication.
- Evidence of the extent to which other recommended add-on treatments would improve these outcomes in patients at Step 4 of the BTS/SIGN guideline is lacking.
- The BTS/SIGN guidelines emphasise a stepwise approach to managing asthma based on control and maintenance of response [2]. The key tiotropium trials do not provide evidence of outcomes on stepping down treatment in patients who achieve control following the addition of tiotropium.

Summary of evidence on cost effectiveness:

Health Technology Assessment bodies in the UK have not yet assessed the cost effectiveness of tiotropium in the treatment of asthma.

A cost effectiveness analysis of tiotropium as an add-on to usual care compared with usual care alone, conducted by the manufacturer of tiotropium from the perspective of the UK NHS, has been published [14]. A Markov model was developed with health states reflecting different levels of asthma control, based on Asthma Control Questionnaire (ACQ) scores, and exacerbation severities estimated from the key tiotropium trial data. Asthma-related mortality is not considered in the base case analysis. Utility values to weight health states were derived from EQ-5D data collected in the trial, with utility weights for exacerbations sourced from the literature. Resource use associated with each health state was based on UK expert clinical opinion. Over a lifetime horizon, the incremental cost per QALY gained for the addition of tiotropium to usual care was estimated to be £21,906 based on additional costs of £5,238 and a gain of 0.24 QALYs. The main driver of the additional costs was the acquisition costs of tiotropium, and the main driver of the QALY gains was a modelled improvement in controlled and partially controlled asthma and in uncontrolled asthma. The model was most sensitive to the assumed costs of uncontrolled asthma.

Key limitations relate to the assumptions that the only change in treatment over the lifetime horizon (of up to 47 years) is in management of exacerbations; all patients, in effect, remain at Step 4 of the treatment guideline, all persist with current maintenance treatment and have the same adherence rates as in the trials. The majority of the modelled patient cohort remains in an uncontrolled asthma state throughout the lifetime horizon, whether they receive tiotropium add-on therapy or not. A lower proportion are modelled to have uncontrolled asthma and a higher proportion are modelled to have partly controlled or controlled asthma if they receive tiotropium add-on therapy [14]. Although the key trials found statistically lower proportions of patients on tiotropium experienced exacerbations of any severity, and severe exacerbations (NNT=15 over 48 weeks of treatment), there were no clinically significant differences in asthma control measured by ACQ scores, or in asthma symptom-free days, or use of rescue medication, from the addition of tiotropium to usual care in the trials [5]. Based on probabilistic sensitivity analysis, which considers the joint uncertainty in the parameter values used in the model, tiotropium had a 45% probability of having an incremental cost per QALY gained below the usual threshold range for cost effectiveness (£20-30,000 per QALY gained) and a 34% probability that it exceeded this range [14].

Prescribing and risk management issues:

- Tiotropium 2.5 micrograms solution for inhalation is licensed for use only in adults who are currently treated with the maintenance combination of high dose ICS and LABA and who experienced one or more severe exacerbations in the previous year. It should be used with caution in those with known cardiac rhythm disorders [4]. The key trials excluded patients with cardiovascular disease [5].
- The dry powder formulation of tiotropium, delivered at a dose of 18 micrograms per day via the HandiHaler® device, is not licensed for use in asthma.
- A high proportion of patients with difficult to control asthma have poor adherence with regular controller therapy, particularly ICS [12,17]. It is therefore imperative that adherence and inhaler technique are assessed before initiating additional agents in patients who remain symptomatic on ICS and LABA therapy.
- In patients who achieve asthma control, the BTS/SIGN guideline promotes a step-down in treatment to the lowest level at which control is maintained [2]. The key clinical trials do not provide evidence to guide a step down in treatment in patients who initiate tiotropium at Step 4 and achieve control. When considering step-down in treatment, it should be noted that ICS is recommended as a preventative therapy in adults at all treatment levels except Step 1 [2], and tiotropium is not licensed for use in patients who are not taking high dose ICS in combination with LABA [4].

Commissioning considerations:

Comparative unit costs:
Table 2 includes costs of tiotropium and example treatments recommended in the BTS/SIGN guideline as possible add-on agents at Step 4 for adults [2]. As many patients in the key tiotropium trials were taking alternative add-on agents as part of their background maintenance treatment at randomisation, tiotropium may be used in addition to, rather than instead of these other add-on agents. An alternative to adding on further agents is to increase the dose of ICS up to a maximum of 2,000 micrograms/day BPD equivalent, but it is not possible to provide cost estimates for that strategy.

Table 2: Example costs of tiotropium and other potential BTS/SIGN Step 4 add-on treatments in adults

Drug	Example regimen	Pack cost	Cost per patient per year (ex VAT)
Tiotropium 2.5 micrograms (Spiriva® Respimat®)	2 sprays once daily in the morning	£33.50 for 60 sprays	£408
LTRA			
Montelukast (Non-proprietary)	10mg once daily in the evening	£2.42 for 28 tabs	£31.46
Zafirlukast (Accolate®)	20mg twice daily	£17.75 for 56 tabs	£230.75
SR Theophylline			
Nueline SA® 250mg	250-500mg every 12 hours	£8.92 for 60 tabs	£109 - £217
Slo-Phyllin® 250mg	250-500mg every 12 hours	£4.34 for 56 caps	£57 - £113
Uniphyllin Continus®	200-400mg every 12 hours	£2.96 for 56 tabs, 200mg £5.65 for 56 tabs, 400mg	£39 - £74
Costs based on mims online accessed 21/11/14 This table does not imply therapeutic equivalence of drugs or doses. LTRA=Leukotriene receptor antagonist; SR=Slow release			

Associated additional costs or available discounts:

None.

Productivity, service delivery, implementation:

Tiotropium has been demonstrated to reduce the incidence of severe exacerbations. For every 15 patients treated with tiotropium for a year, one severe exacerbation requiring treatment with systemic corticosteroids would be avoided [5]. There was no reduction in asthma-related hospitalisations.

Anticipated patient numbers and net budget impact:

The BTS/SIGN guidelines note there are no precise data on the prevalence of difficult-to-treat asthma, defined as requiring a treatment level of at least Step 4 [2]. ePACT prescribing data are of limited value in estimating potential patient numbers as they are not linked to therapeutic indication; ICS plus LABA may be used in patients with COPD, in addition to patients with asthma.

Based on Quality and Outcomes Framework asthma registry data for April 2013-March 2014 [15], and Asthma UK figures that indicate 79.6% of treated asthma patients are adults [16], a crude estimate of the number of adult patients with asthma in each CCG in Lancashire can be made. A published literature review reports 5-10% of asthma cases are difficult to treat asthma [16]. Assuming this represents the proportion of patients at Step 4 of the BTS/SIGN treatment pathway, the number of adult patients potentially eligible for treatment with tiotropium at Step 4 in each CCG is presented in Table 3.

These figures represent crude prevalence estimates of adult patients at Step 4. It is not possible to determine the proportion of patients that would receive tiotropium, as this will be determined by a range of factors. Therefore, the potential budgetary impact of the use of tiotropium at hypothetical levels of uptake is provided for illustration only. As many patients in the key trials were already taking alternative Step 4 add-on agents, tiotropium costs may be additional to those of other add-on treatments, rather than displacing these.

CCGs	No. adult pts at BTS/SIGN Step 4*	Tiotropium acquisition cost at 10% uptake (£) (ex. VAT)	Tiotropium acquisition cost at 50% uptake (£) (ex. VAT)
NHS BLACKBURN WITH DARWEN CCG	486 – 973	19,548 – 39,095	97,738 – 195,476
NHS BLACKPOOL CCG	478 – 956	19,218 – 38,436	96,089 – 192,179
NHS CHORLEY AND SOUTH RIBBLE CCG	454 – 908	18,250 – 36,499	91,248 – 182,495
NHS EAST LANCASHIRE CCG	1,037 – 2,074	41, 685 – 83,370	208,424 – 416,894
NHS GREATER PRESTON CCG	519 – 1,039	20,874 – 41,749	104,372 – 208,744
NHS LANCASHIRE NORTH CCG	422 – 844	16,955 – 33,909	84,773 – 169,547
NHS WEST LANCASHIRE CCG	284 – 567	11,398 – 22,795	56,988 – 113,976
NHS FYLDE & WYRE CCG	404 – 808	16, 241 – 32,482	81,204 – 162,408
ALL CCGs	4,084 – 8,168	164,167 – 328,335	820,837 – 1.64million
*Based on 76.9% of asthma patients being adult, and 5-10% being difficult to treat			

Table 3. Potential numbers of asthma patients eligible for tiotropium treatment in an average CCG, and tiotropium acquisition costs at hypothetical levels of uptake

Innovation, need, equity:

Tiotropium use in this patient cohort is not innovative as it has been used extensively in COPD for many years and has been trialled in a subset of asthma patients with clinical features similar to COPD. Despite improving severe exacerbation incidence, there was no reduction in asthma hospitalisations, or symptom free days or use of rescue medication, and patients did not report a significant improvement in symptom control or quality of life with tiotropium compared with placebo. Evidence that tiotropium is innovative relative to the alternative agents at Step 4 is lacking.

Patients at Step 4 of the BTS/SIGN guideline treatment pathway have, by definition, difficult to control asthma. A range of add-on treatments are available and recommended (although clinical trial data to guide management of these patients are lacking).

No equity issues are anticipated.

References

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Table 1: Summary of key tiotropium (Spiriva® Respimat®) RCTs relevant to use in adults with asthma

Ref	Trial design	Patients / Trial subjects	Trial intervention and comparison	Outcomes: Primary endpoints [FAS/PP]	Outcomes: Key secondary / exploratory endpoints	Grading of evidence / risk of bias
[5]	Two replicate, phase 3, 48-week, randomised, double-blind, placebo-controlled, parallel-group trials. Inclusion criteria: • Adults • Asthma for at least 5 years diagnosed before age 40 • Non-smokers / smoking history <10pack-years • Symptomatic, score of ≥1.5 on ACQ-7, • Persistent airflow limitation, post bronchodilator FEV_1 ≤80% and FVC ≤70% predicted • ≥1 exacerbation in last year • On ICS dose ≥800 micrograms budesonide equivalent /day and on LABA, ≥1 exacerbation treated with systemic steroids in previous	• Mean age: 53 yrs • Female: 60.4% • White: 83% • Never smokers: 76% • Median asthma duration: 28 yrs • Severe* exacerbations in last year: <3 (81%) 3-5 (14%) >5 (5%) • Mean ACQ-7: 2.6 • Mean AQLQ: 4.6 • Pre bronchodilator FEV1: 1.6L • Post bronchodilator FEV1 % predicted: 62% • FVC: 2.7L • FEV1/FVC ratio: 57.8% • Median ICS dose: 800 micrograms/day (interquartile range 800-1600 micrograms) • Medication at randomisation: Maintenance oral steroids: 5.3%	Trial 1: Tiotropium 5 micrograms om (n=237; 211 completed study) Placebo om (n=222; 202 completed study) All delivered via Respimat ®device	Co-primary endpoints: i) Difference (tiotropium-placebo) in change from baseline in peak $FEV_{1\ (0\text{-}3h)}$ at 24 weeks: 86mL (95%CI: 20 to 152); p<0.05 ii) Difference (tiotropium-placebo) in change from baseline in trough FEV_1 at 24 weeks: 88ml (95%CI: 27 to 149); p<0.01	Difference (tiotropium-placebo) in change from baseline in: Peak $FEV_{1\ (0\text{-}3h)}$ at 48 weeks: 73mL (95%CI: 5 to 140); p<0.05 Trough FEV_1 at 48 weeks: 42ml (95%CI: -21 to 104); p=NS ACQ-7 score, 24 weeks: -0.13; p=NS AQLQ score, 24 weeks: 0.04, p=NS Number of asthma symptom free days, 24 weeks: -0.01; p=NS Rescue medication use (puffs per day), 24 weeks: -0.09; p=NS	POO measure?: Yes – time to first severe exacerbation is a co-primary endpoint and trials also assessed QoL and asthma symptom control Allocation concealment?: Yes Blinded if possible?: Yes, double blind Intention to treat analysis?: No, FAS/PP Adequate power/size?: Yes Adequate follow-up (>80%)?: Yes, 89% Risk of bias (related to internal validity of the trial): likely to be low Level 1 or 2 evidence based on fact that not ITT analysis (but number of patients in the FAS is 907 vs. 912

	year • Other medication stable Exclusion criteria: • COPD diagnosis • CV disease • Other serious coexisting illness	Theophylline: 16.7% LTRA: 22.3% Antihistamine: 14.7%	Trial 2: Tiotropium 5 micrograms om (n=219; 198completed study) Placebo om (n=234; 203 completed study) All delivered via Respimat ®device	Co-primary endpoints: i) Difference (tiotropium-placebo) in change from baseline in peak $FEV_{1\ (0\text{-}3h)}$ at 24 weeks: 154mL (95%CI: 91 to 217); p<0.001 ii) Difference (tiotropium-placebo) in change from baseline in trough FEV_1 at 24 weeks: 111ml (95%CI: 53 to 169); p<0.001	Difference (tiotropium-placebo) in change from baseline in: Peak $FEV_{1\ (0\text{-}3h)}$ at 48 weeks: 152mL (95%CI: 87 to 217); p<0.001 Trough FEV_1 at 48 weeks: 92ml (95%CI: 32 to 151); p<0.01 ACQ-7 score, 24 weeks: -0.20 (95%CI: -0.3 to -0.07); p<0.01 AQLQ score, 24 weeks: 0.18 (95%CI: 0.03 to 0.33); p<0.05 Number of asthma symptom free days, 24 weeks: 0.08; p=NS Rescue medication use (puffs per day), 24 weeks: -0.26; p=NS	that could be in the ITT population, and balanced across arms so unlikely to create significant bias)
			Pooled results	Co-primary endpoint: iii) Time to first severe* asthma exacerbation – pooled across both trials: 282 days vs. 226 days HR 0.79 (95%CI 0.62 to 1.00); p=0.03 (NB: <50% of patients experienced exacerbation; median time to first exacerbation cannot be calculated)	Tiotropium vs. placebo at 48 weeks: % patients with ≥1 episode of asthma worsening†: 49.9% vs. 63.2%; p<0.001 % patients with ≥1 severe* exacerbations: 26.9% vs. 32.8%; p<0.05 Severe* exacerbations per patient-year: 0.530 vs. 0.663; p=0.046 % patients with ≥1 asthma hospitalisation: 3.5% vs. 4.4%; p=NS	

†Asthma worsening defined as: progressive increase in symptoms (as compared with usual day-to-day asthma symptoms) or a decline of ≥30% in the best morning PEF from the mean screening morning PEF for 2 or more consecutive days.
* Severe exacerbation defined as: deterioration of asthma necessitating initiation or at least a doubling of systemic glucocorticoids for ≥3 days. Measured as the time until at least 25%

of patients had a first severe exacerbation.
AQLQ=Asthma quality of life questionnaire, 32 questions scores on scale 1 (severely impaired) -7 (no impairment) with 0.5 unit minimal clinically important difference; ACQ-7=Asthma control questionnaire with 7 questions, score range 0-6 with 0.5 unit minimal clinically important difference; FAS=Full analysis set - includes all randomised patients who received at least 1 dose and had one efficacy measure (n/N randomised =907/912); FEV_1=Forced expiratory volume in 1 second; Peak $FEV_{1\ (0\text{-}3h)}$= Peak FEV1 in the first 3 hours after dosing; FVC=Forced vital capacity; LTRA=Leukotriene receptor antagonist; NS= not statistically significant; om=every morning; PEF=Peak expiratory flow; PP=Per protocol analysis (n/N=912/912)

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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