Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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tiotropium, 2.5 microgram, solution for inhalation (Spiriva® Respimat®)

SMC No. (1028/15)

Boehringer-Ingelheim Limited

10 July 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

tiotropium (Spiriva® Respimat®) is accepted for use within NHS Scotland.

Indication under review: 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 $beta_2$ agonists and who experienced one or more severe exacerbations in the previous year.

Two phase III RCTs demonstrated that the addition of tiotropium significantly improved lung function and increased the time to the first severe exacerbation compared with placebo in patients with uncontrolled asthma despite treatment with high dose inhaled corticosteroid and a long acting $beta_2$ agonist.

Overleaf is the detailed advice on this product.

Vice Chairman,
Scottish Medicines Consortium

Indication

As add-on maintenance bronchodilator treatment in adult patients with asthma who are currently treated with the maintenance combination of inhaled corticosteroid (ICS) (≥800 micrograms budesonide/day or equivalent) and long-acting beta$_2$ agonists (LABA) and who experienced one or more severe exacerbations in the previous year.

Dosing Information

5 micrograms tiotropium given as two puffs from the Respimat® inhaler once daily, at the same time each day.

Product availability date

01 October 2014

Summary of evidence on comparative efficacy

Tiotropium is a long acting muscarinic antagonist (LAMA) that relaxes the bronchial smooth muscle by binding competitively and reversibly to muscarinic receptors and inhibiting the bronchoconstrictive effects of acetylcholine.[1] Tiotropium is currently available as a treatment for chronic obstructive pulmonary disease.

The evidence to support this new indication is from two identically designed phase III, randomised, double-blind, placebo-controlled studies, PrimoTinA 1 and 2. The studies recruited patients aged 18 to 75 years with ≥5 year history of asthma diagnosed before the age of 40 years. They had severe persistent asthma and were symptomatic despite treatment with a high, stable dose of inhaled corticosteroid (ICS) and a LABA for ≥4 weeks before the screening visit. The term "symptomatic" was defined as a mean score of ≥1.5 on the Asthma Control Questionnaire and forced expiratory volume in one second (FEV1) ≤80% of predicted normal and ≤70% forced vital capacity (FVC) 30 minutes after inhalation of 400 micrograms salbutamol. Other inclusion criteria were a history of at least one severe asthma exacerbation in the previous year; non-smoker or a smoking history of ≤10 pack-years.[2,3]

After a 4-week screening period patients were randomised equally to receive 48 weeks treatment with once daily inhaled tiotropium 5 micrograms or placebo (study 1: n=237 versus n=222; study 2: n=219 versus n=234). Study drug was added to the combination of high-dose ICS (≥800 micrograms of budesonide or equivalent) and a LABA. Permitted concomitant medicines included stable doses of sustained-release (SR) theophylline, leukotriene receptor antagonists (LTRAs), omalizumab and oral glucocorticosteroids (≤5mg prednisolone equivalent per day). Inhaled salbutamol was provided as rescue treatment. [2]

There were three co-primary outcomes and all were evaluated in the full analysis set, defined as all treated patients who had baseline data and at least one on-treatment efficacy measurement. Two primary outcomes were lung-function end points, peak FEV1 (within 3 hours after administration of the maintenance and study medication) and trough FEV1 response both expressed as the change from baseline FEV1 and measured at 24 weeks. The third co-primary outcome was symptom based: time to first severe asthma exacerbation (defined as a deterioration of asthma necessitating initiation or at least a doubling of systemic glucocorticosteroids for ≥3 days), which was evaluated from 48-week pooled study data.[2]

In both studies tiotropium was associated with a significant improvement in change from baseline FEV1 when compared with placebo at 24 weeks (primary outcomes).[2]

Results for forced expiratory flow in 1 second (FEV1)

	Study 1		Study 2	
	Number of patients	Adjusted mean change from baseline: Tiotropium minus placebo	Number of patients	Adjusted mean change from baseline: Tiotropium minus placebo
Peak FEV1 at 0 to 3 hr mL (95% CI)				
24 weeks	428	86 (20 to 152) p<0.05	423	154 (91 to 217) p<0.001
48 weeks	417	73 (5 to 140) p<0.05	403	152 (87 to 217) p<0.001
Trough FEV1 mL (95% CI)				
24 weeks	428	88 (927 to 149) p<0.01	422	111 (53 to 169) p<0.001
48 weeks	417	42 (-21 to 104) NS	402	92 (32 to 151) p<0.01

FEV1= forced expiratory volume in one second; CI=confidence interval; NS=non-significant

Significant improvement over placebo in peak FEV1 was sustained to 48 weeks in both studies but improved trough FEV1 was sustained to 48 weeks in Study 2 only.

The third co-primary endpoint, time to first severe asthma exacerbation, (pooled 48 week data) found that 27% (122/453) of tiotropium patients and 33% (149/454) of placebo patients had experienced a severe exacerbation. Time to first severe exacerbation was increased by 56 days with tiotropium (282 days versus 226 days with placebo), a risk reduction of 21% (Hazard Ratio [HR] 0.79; 95% CI 0.62 to 1.00; p=0.03).[2]

Median time to first worsening of asthma (pre-specified as the time to first [any] exacerbation) was evaluated as a secondary outcome from the pooled 48-week data. This was increased by 134 days with the addition of tiotropium; 315 days for tiotropium patients versus 181 days for placebo patients (HR 0.69 95% CI: 0.58 to 0.82; p<0.001). Improvements in weekly morning and evening peak expiratory flow values (recorded by the patient) were significantly greater in the tiotropium group than in the placebo group and were sustained to 48 weeks.

There was no difference between tiotropium and placebo in use of rescue medication at 24 weeks. Two patient reported outcomes were measured: the Asthma Control Questionnaire and the Asthma Quality of Life Questionnaire. Both consist of 7-point scales with a minimum clinically important difference of 0.5 units. There was improvement in both studies but neither study showed a clinically meaningful difference between tiotropium and placebo.[3]

Summary of evidence on comparative safety

The overall safety profile of tiotropium is consistent with the known class effect of LAMAs. In the pooled PrimoTinA studies, adverse events were reported in 74% of the tiotropium group and 80% in the placebo group. Drug-related adverse events were reported in 5.7% (26/456) of patients in the tiotropium group and 4.6% (21/456) in the placebo group. Allergic rhinitis was the only adverse event that occurred at a significantly higher rate in the tiotropium group. Dry mouth was reported in eight (1.8%) patients in the tiotropium group and three (0.7%) patients in the placebo group.[2]

Serious adverse events were reported in similar proportions of patients in each treatment group, 8.1% (37/456) in the tiotropium group and 8.8% (40/456) in the placebo group. Three serious adverse events (all in the tiotropium group) were considered to be life-threatening. Two patients had an asthma exacerbation and recovered fully, one patient had a cerebral infarction.

The Medicines and Healthcare Products Regulatory Agency issued a Drug Safety Update in February 2015 advising that there was no significant difference in mortality in the TIOSPIR chronic obstructive pulmonary disease study when tiotropium was delivered via Respimat® compared with Handihaler®. It recommended that the risk of cardiovascular side effects be taken into account when prescribing tiotropium delivered via Respimat® or Handihaler® to patients with certain cardiac conditions, who were excluded from clinical studies of tiotropium (including TIOSPIR).[6]

Summary of clinical effectiveness issues

The indication under review for tiotropium is as add-on therapy in adult patients with asthma who are currently treated with a maintenance combination of ICS and LABA and who are still uncontrolled having experienced one or more severe exacerbations in the previous year. The British Thoracic Society/Scottish Intercollegiate Guidelines Network (SIGN) guidelines recommend increasing the ICS dose or the addition of a fourth drug e.g. leukotriene receptor antagonist, SR theophylline or oral LABA.[7]

Clinical experts consulted by SMC considered that there is unmet need in the treatment of asthma and that many patients have poorly controlled symptoms despite combination treatment with ICS and LABA. They advised that tiotropium offers a new treatment option for the patient population under review but that it is unlikely to displace any specific treatment and would probably be an additional add-on therapy in patients with difficult and severe asthma. Tiotropium is the first LAMA to be licensed in the UK for asthma.

Two identical, well conducted, phase III, randomised controlled studies demonstrated that tiotropium as add-on therapy to high dose ICS and LABA has a modest beneficial effect over placebo on lung function demonstrated by improvement in peak and trough FEV1 at 24 weeks in patients with severe, persistent asthma and improvement in peak FEV1 was sustained to 48 weeks. Of note, the trial population were permitted use of stable concomitant medicines including bronchodilator therapy (SR theophylline and LTRAs) in addition to LABA use in all patients. The symptom based endpoint, (using pooled analysis at 48 weeks) of time to first severe asthma exacerbation, showed a risk reduction of 21% compared with placebo. Longer

studies would be beneficial to determine the long term effect on asthma exacerbations. Tiotropium did not demonstrate benefits over placebo in the requirement for rescue medication or achievement of a clinically meaningful benefit in asthma related quality of life.

There are no studies directly comparing tiotropium with alternative add-on therapies recommended in current asthma guidelines for patients uncontrolled on ICS and inhaled LABA e.g. leukotriene receptor antagonists, SR theophylline and oral LABA.

Summary of comparative health economic evidence

The company presented a cost-utility analysis of tiotropium in adult patients with asthma as add-on therapy in patients receiving bronchodilator treatment which included a maintenance combination of ICS and LABA. A Markov model was used in the analysis which consisted of six health states (three asthma control and three exacerbation health states) and death as an absorbing health state. Patients were categorised into each asthma control health state according to their Asthma Control Questionnaire score. A lifetime horizon was used in the analysis. SMC clinical experts noted that whilst other add-on treatments are used in practice, it is unlikely that these medicines would be displaced by the introduction of tiotropium.

The clinical evidence used to support the economic analysis was taken from the pooled results of the PrimoTinA studies, 1 and 2 described above. The data from the secondary outcome measure of Asthma Control Questionnaire change from baseline were used to define the asthma control states and derive transition probabilities within the model. Based on the pooled results of these studies, tiotropium resulted in a statistically significant improvement compared with placebo in change from baseline Asthma Control Questionnaire score at both 24 and 48 weeks.

Drug costs were included in the analysis which consisted of tiotropium, ICS and LABA treatment costs. Adverse event costs were not included as the treatments were assumed to have similar safety profiles. The costs of concomitant medications were also considered and the quantity of co-medication consumed was dependent on the patient's health state but assumed to be equal in both arms. Non-drug costs including hospitalisations, outpatient visits, home visits and laboratory tests and procedures were also included in the analysis and calculated based on the weighted cost per cycle.

Utility values for the asthma control health states were derived from the clinical studies using the EQ-5D questionnaire. In order to align patients' EQ-5D scores to each of the asthma control health states, the EQ-5D scores were matched according to patients' Asthma Control Questionnaire score. The company used the average EQ-5D values at the 9th visit (week 48) as the utility weights. Published literature was used to estimate the utilities for exacerbation health states, however, the value for the non-severe exacerbation, was based on assumption i.e. the average between uncontrolled asthma health state and severe exacerbation without hospitalisation.

The base case results reported an incremental cost effectiveness ratio (ICER) of £22,487 per quality-adjusted life-year (QALY) based on an incremental cost of £4,849 and an incremental QALY gain of 0.22. The incremental cost associated with tiotropium is primarily due to the cost of treatment, as tiotropium is an add-on treatment to ICS and LABA. In addition, patients on tiotropium remain in the asthma control health states for a longer time period versus patients

receiving ICS and LABA alone. The 0.22 QALY gain associated with tiotropium is largely due to the longer time spent in the optimal control health state.

The company provided a range of sensitivity analyses including one-way, scenario and probabilistic sensitivity analysis. The scenario analysis tested a number of assumptions, for example when mortality associated with hospitalisations due to severe exacerbations was included the ICER decreased to £18,279. When the difference in utilities between the acceptable control and severe exacerbation (without hospitalisation) health states was reduced by 20%, and a reduced time horizon of 20 years was assumed, the ICER increased to £25,046 per QALY, based on an incremental cost of £3,737 and an incremental QALY gain of 0.15.

The following weaknesses were noted:

- As the transition probabilities in the model were based on averaged weekly probabilities from week 1 to 9 and 9 to 48, there is some uncertainty surrounding long term efficacy. For completeness the company was asked to use transition probabilities from week 47 to 48, as these were considered to be more reflective of long term efficacy. The analysis has subsequently been provided and resulted in a lower ICER (£6k), but the company noted this result should be interpreted with caution due to the low number of patients transitioning at this stage. However, the sensitivity analysis on the time horizon does provide a test of the uncertainty associated with the longer term extrapolation and the ICER remained below £30k when shorter time horizons were used.

- The values for the asthma control health states i.e. optimal and acceptable control health states appear to be high relative to values identified in relevant published studies. In order to address some uncertainty surrounding these values the company provided a more conservative combined analysis in which both the time horizon and the utility values for the optimal and acceptable asthma control health states were reduced. Based on this analysis tiotropium resulted in ICERs of £26,338, £27,514 and £29,131 over a 20 year, 15 year and 10 year time horizon respectively.

- The pooled analysis demonstrated that tiotropium was associated with a statistically significant difference in Asthma Control Questionnaire score versus placebo at both 24 and 48 weeks, however this difference was less than the minimum clinically important difference of 0.5 units. Therefore, there was some concern that the benefit experienced by patients in the economic model may have been overestimated. However, the uncertainty surrounding treatment effect has been addressed by the additional analysis provided by the company.

Despite the weaknesses outlined above, the economic case has been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- A submission was received from Asthma UK, a registered charity.

- Asthma UK has received pharmaceutical company funding in the past two years including from the submitting company.

- Asthma is one of the most common long-term conditions in the UK. For some people with asthma, their symptoms remain uncontrolled despite treatment with high-dose inhaled steroids (ICS) in addition to Long Acting Beta Agonists (LABA). For these patients, their asthma symptoms can lead to poor quality of life (time off work / school, frequent hospital attendances or admissions, side effects from prolonged use of steroids and inability to lead a mobile and active lifestyle) and even death.

- For most patients, current treatments suffice. However, for some people, they remain uncontrolled despite ICS and LABA treatments because they are resistant to current therapies. For these people, they rely on daily steroid tablets and even novel biological therapies. Side effects from prolonged oral steroid use and time off to receive intravenous care in hospital (for those on biological therapy) can have a large impact on quality of life.

- Tiotropium would give these patients another treatment option with evidence of efficacy and tolerability that may help them control their symptoms more effectively to prevent potentially life-threatening asthma attacks.

Additional information: guidelines and protocols

British Thoracic Society & Scottish Intercollegiate Guideline Network SIGN 141 British guideline on the management of asthma was published in October 2014[7]
(Adult doses cited)

- Step 1: mild intermittent asthma – inhaled short-acting beta agonists (SABA) as required.
- Step 2: regular preventer therapy; add inhaled corticosteroid (ICS) 200 to 800 micrograms/day budesonide dipropionate or equivalent.
- Step 3: Add inhaled long acting beta agonist (LABA);
  If response to LABA is good – continue LABA.
  If response to LABA is present but insufficient – continue LABA and increase/maintain ICS dose at 800 micrograms/day.
  If response to LABA is absent – stop LABA and increase ICS dose to 800 micrograms/day and if control still inadequate, institute trial of e.g. leukotriene receptor antagonist or SR theophylline
- Step 4: Persistent poor control
  Consider sequential trials of: increasing ICS to 2,000 micrograms/day; addition of a fourth drug e.g. leukotriene receptor antagonist, SR theophylline, oral LABA.
  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.
- Step 5: Continuous or frequent use of oral steroids.

Global Initiative for asthma (GINA) Revised 2014 (preferred choice of controller treatment only shown)

- Step 1: As needed SABA.
- Step 2: Low dose ICS.
- Step 3: Low dose ICS/LABA.
- Step 4: med/high dose ICS/LABA

- Step 5: refer for add-on treatment e.g. anti-IgE.[8]

Additional information: comparators

Other treatments that may be used in the population under review are leukotriene receptor antagonists (montelukast, zafirlukast), SR theophylline (e.g. Slo-Phyllin®)and oral LABAs (e.g. modified release salbutamol and bambuterol).

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Tiotropium (Spiriva® Respimat®)	**5 micrograms once daily (inhaled)**	**406**
Montelukast	10mg once daily (oral)	33
Zafirlukast	20mg twice daily (oral)	231
Bambuterol	10mg to 20mg once daily (oral)	188 to 205
Salbutamol SR	8mg twice daily (oral)	126
Theophylline MR (Slo-Phyllin®)	250mg to 500mg twice daily (oral)	56 to113

MR=modified release; SR=sustained release. Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis 21 April 2015

Additional information: budget impact

The submitting company estimated the population eligible for treatment with tiotropium to be 73,876 in year 1 rising to 81,922 in year 5 with an estimated uptake rate of 1% (739 patients) in year 1 rising to 13% (10,650 patients) in year 5.

The gross impact on the medicines budget was estimated to be £301k in year 1 and £4.3m in year 5. As no other medicines are expected to be displaced the net medicines budget impact is the same as the gross estimate.

SMC clinical expert responses indicate that treatment uptake is likely to be higher in practice than estimated by the company.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Tiotropium 2.5 microgram solution for inhalation (Spiriva® Respimat®) Summary of product characteristics. Boehringer-Ingelheim Ltd. Last accessed 13.01.2015

2. Kerstjens HA. Engel M. Dahl R. et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med Sept 2012; 367: 1198-207

3. Kerstjens HA. Engel M. Dahl R. et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med 2012; 367: 1198-207 supplement updated Dec 2012

4. clinicaltrials.gov website NCT00772538

5. clinicaltrials.gov website NCT00776984

6. Medicines and Healthcare Products Regulatory Agency Drug Safety Update 16 February 2015

7. British guideline on the management of asthma. British Thoracic Society and Scottish Intercollegiate Guideline Network. October 2014

8. Global initiative for asthma (GINA) guidelines. Revised 2014

This assessment is based on data submitted by the applicant company up to and including 11 June 2015.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.