AWMSG Secretariat Assessment Report – Limited submission

Tiotropium (Spiriva® Respimat®) 2.5 microgram, inhalation solution

Company: Boehringer Ingelheim Ltd

Licensed indication under consideration: add-on maintenance bronchodilator treatment in patients aged 6 years to < 18 years with severe asthma who experienced one or more severe asthma exacerbations in the preceding year

Date of licence extension: 12 April 2018

Comparator(s)

The company stated that there is no comparator and that tiotropium (Spiriva® Respimat®) is an add-on treatment.

Limited submission details

- The limited submission criteria were met based on a minor licence extension.

Clinical effectiveness

- Tiotropium (Spiriva® Respimat®) was recommended by the All Wales Medicines Strategy Group in 2017 as an add-on maintenance bronchodilator treatment in adult patients with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (≥ 800 micrograms budesonide per day or equivalent) and long-acting β2 agonists and who experienced one or more severe exacerbations in the previous year. This submission covers the licence extension to include patients aged 6 years to < 18 years. The whole licenced indication wording was revised at the time of the paediatric licence extension and is now the same for adults and children; the specification of inhaled corticosteroid dose and the number of concomitant controller medicines has been moved to Section 4.2 of the Summary of Product Characteristics.
- The updated licence specifies that tiotropium should be used in addition to inhaled corticosteroids and one or two controllers; the number of controllers is related to the dose of inhaled corticosteroid. In line with these specifications, the company expects tiotropium to be used as an add-on treatment option at the "high-dose therapies" step of the British Thoracic Society and Scottish Intercollegiate Guidelines Network (BTS/SIGN) guideline on the management of asthma. The company state that there are no comparators. Clinical expert opinion sought by AWTTC supports the company's suggested place in the treatment pathway, indicating that tiotropium might be used after all other add-on therapies have been tried or as an add-on to inhaled corticosteroids plus a long-acting β2 agonist (i.e. one controller); in the latter case, tiotropium would be used as an alternative to theophylline or potentially as an alternative to a leukotriene receptor antagonist.
- The company submission includes two double-blind, randomised, phase III studies comparing the efficacy and safety of tiotropium (5 micrograms and 2.5 micrograms once daily) add-on therapy to inhaled corticosteroids plus one or more controller

therapies, to placebo. Patients were eligible for inclusion if they were symptomatic despite maintenance treatment with a combination of high-dose inhaled corticosteroid and one or more controller therapy or medium-dose inhaled corticosteroid and two or more controller therapies. Patients were aged between 6 and 11 years (study 205.446) or 12 and 17 years (study 205.456). The primary endpoint was the change from baseline in peak forced expiratory volume in one second within three hours after dosing, after 12 weeks of treatment. Tiotropium (5 micrograms) statistically significantly improved the primary endpoint compared with placebo in patients aged 6 to 11 years, with only a numerical improvement (not statistically significant) observed in patients aged 12 to 17 years. The company state that regulators agreed tiotropium 5 micrograms once daily (the licensed dose) to be efficacious in patients aged 6 to 17 years on the basis of the results from studies 205.446 and 205.456 taken together with results from phase II and III studies of tiotropium across a range of ages (including adults) and disease severities in the full clinical development programme.

- The definitions of high and medium inhaled corticosteroid doses in studies 205.446 and 205.456 do not entirely align with those in the BTS/SIGN asthma guideline. However, the inhaled corticosteroid doses and their corresponding number of controller therapies specified in the tiotropium licence do align with the "high-dose therapies" step of the BTS/SIGN guideline.
- The company performed a meta-analysis of studies 205.446 and 205.456 and compared the results with pooled analyses of two similar studies in adults (studies 205.416 and 205.417). The results suggested similar efficacy of tiotropium in adults and patients aged 6 to 17 years with regard to pulmonary function and time to first exacerbation. Results for the risk of experiencing a severe exacerbation in patients aged 6 to 17 years were not statistically significant, possibly due to the short study duration and low number of severe exacerbations.
- In studies 205.446 and 205.456, the safety and tolerability of tiotropium was comparable to placebo and no new safety signals were identified. This is consistent with the safety profile reported in adults.
- Tiotropium is administered by the Respimat® inhaler. The company submission includes data to support the ease of use and handling of this inhaler by children and adolescents.

Budget impact

- The company estimates that there will be 4,311 patients aged 6 to 17 years per year with severe asthma eligible for treatment with tiotropium; this is based on Welsh population age estimates, Welsh disease registers and UK data on the proportion of patients (aged 5–15 years) at the "high-dose therapies" step or above of the BTS/SIGN guidelines.
- The company estimates that uptake will be [commercial in confidence figure removed] in Year 1, rising to [commercial in confidence figure removed] in Year 5. This equates to [commercial in confidence figure removed] patients in Year 1 and [commercial in confidence figure removed] patients in Year 5. Uptake is based on an assumption and therefore is subject to uncertainty. The company considers these to be conservative estimates, based on prescribing data in adults indicating low rates of usage (< 1%).
- [Commercial in confidence information removed].
- The budget impact is based on medicine acquisition costs and does not consider associated administration and monitoring costs. The company assumes that these costs are insignificant and that this is likely a conservative assumption as the meta-analysis showed a reduced rate of exacerbations with tiotropium compared with placebo.

- The budget impact assumes that no medicines are displaced. Clinical expert opinion sought by AWTTC suggests tiotropium may be used as an alternative to theophylline, but also potentially as an alternative to a leukotriene receptor antagonist. If these medicines are displaced, the estimated budget impact is likely to be an overestimate.

Additional information

- AWTTC is of the opinion that, if recommended, tiotropium (Spiriva® Respimat®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

Evidence search

Date of evidence search: 15 August 2018
Date of range of evidence search: No date limits were applied to database searches.

Further information

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTC at AWTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Tiotropium (Spiriva® Respimat®) 2.5 microgram, inhalation solution. Reference number: 1882. October 2018.

Appendix: Previous AWMSG secretariat assessment report (published September 2017)

In September 2017, AWMSG appraised tiotropium (Spiriva® Respimat®) as an add-on maintenance bronchodilator treatment in adult patients with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (≥ 800 micrograms budesonide daily or equivalent) and long-acting beta2-agonists and who experienced one or more severe exacerbations in the previous year (AWTTC reference number 3436). This advice is now incorporated into the Final Appraisal Recommendation (FAR) of tiotropium (Spiriva® Respimat®) as add-on maintenance bronchodilator treatment in patients aged 6 years and older with severe asthma who experienced one or more severe asthma exacerbations in the preceding year (AWTTC reference number 1882).

The original report for AWTTC reference number 3436 is included below for completeness.

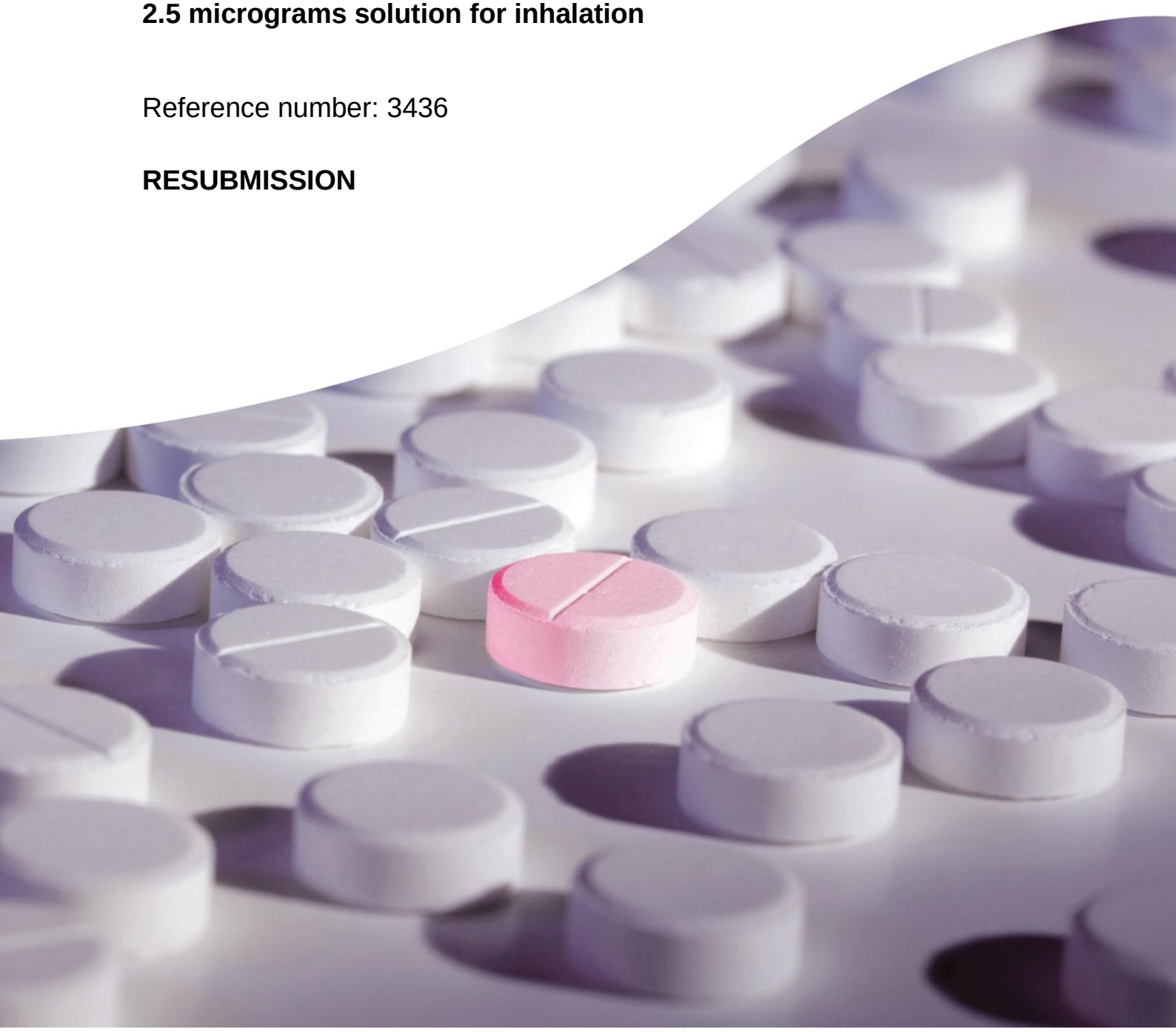
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Tiotropium (Spiriva® Respimat®) 2.5 micrograms solution for inhalation

Reference number: 3436

RESUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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Reference number: 3436. September 2017.

AWMSG Secretariat Assessment Report
Tiotropium (Spiriva® Respimat®) 2.5 micrograms solution for inhalation

This assessment report is based on evidence submitted by Boehringer Ingelheim Limited[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Tiotropium (Spiriva® Respimat®) as an add-on maintenance bronchodilator treatment in adult patients with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (≥ 800 micrograms budesonide daily or equivalent) and long-acting beta2-agonists and who experienced one or more severe exacerbations in the previous year[2]. Refer to the Summary of Product Characteristics (SPC) for the full licensed indication[2].
Dosing	The recommended dose for adults is the delivered dose of five micrograms tiotropium given as two puffs from the Respimat® inhaler once daily, at the same time of the day[2].
Marketing authorisation date	13 September 2014[2] (originally licensed as a maintenance bronchodilator to relieve symptoms of patients with chronic obstructive pulmonary disease [COPD] on 1 October 2007[2]).

2.0 DECISION CONTEXT

2.1 Background

Asthma is a long-term lung disease affecting people of all ages, in which inflammation and narrowing of the airways leads to breathlessness, chest tightness, coughing and wheezing[3]. Asthma episodes can be triggered by viral respiratory infections, exercise, smoke, cold, and allergens such as pollen, mould, animal fur and house dust mites[4]. Asthma exacerbations can be life-threatening in severe cases[4]. The disorder is diagnosed by symptoms and lung function tests, which measure peak expiratory flow (PEF; see Glossary) rate or the forced expired volume in one second (FEV_1; see Glossary)[4]. During 2015–2016, there were 222,590 people in Wales with asthma[5]. The estimated incidence of asthma in Wales is 0.83%[5]. Asthma is responsible for a large number of accident and emergency attendances and hospital admissions[6]. There were 3,568 hospital admissions in Wales for asthma during 2015–2016[7]. In 2015, there were 71 deaths in Wales where the underlying cause was asthma[8].

Tiotropium (Spiriva® Respimat®) is the first licensed long-acting muscarinic antagonist (LAMA) for use as an add-on maintenance bronchodilator in asthma[9]. It works by opening the airways by relaxing the muscles that surround them[10].

Asthma treatment follows a stepwise approach[11,12]. In the British Thoracic Society/Scottish Intercollegiate Network (BTS/SIGN) guideline, if control remains inadequate on a low dose of an inhaled corticosteroid (ICS) plus a long-acting beta2-agonist (LABA) and there has been an improvement when a LABA was added, a LAMA or leukotriene receptor antagonist (LTRA) or slow-release (SR) theophylline is recommended as add-on therapy. Another

treatment option at this stage is to continue the LABA and increase the dose of the ICS. If there has been no response to the LABA being added, the LABA should be stopped and a LTRA or LAMA (unlicensed in this indication) added, or the LABA stopped and the ICS dose increased[11].

The BTS/SIGN guideline recommends increasing the ICS up to a high dose or adding in treatment with a fourth drug at the high-dose therapies stage if control remains inadequate on a medium dose of an ICS plus a LABA. Treatment options to add in are either a LAMA, LTRA, SR theophylline or a beta2-agonist. The guidelines recognise that the potential for side effects is greater with theophyllines and SR beta2-agonist tablets[11].

The All Wales Medicines Strategy Group (AWMSG) has previously appraised tiotropium (Spiriva® Respimat®) for this indication and issued a non-recommendation[13]. A resubmission has been made for tiotropium (Spiriva® Respimat®) to reflect the update to the BTS/SIGN guideline, and with a revised list price[1].

2.2 Comparators

The applicant company states that there is no relevant comparator[1].

2.3 Guidance and related advice

- Global Initiative for Asthma. Global strategy for asthma management and prevention (2017)[12].
- British Thoracic Society/Scottish Intercollegiate Guidelines Network. SIGN 153. British guideline on the management of asthma. A national clinical guideline (2016)[11].
- National Institute for Health and Care Excellence. Quality Standard 25 (QS25). Asthma (2013)[6].
- National Institute for Health and Care Excellence. Technology Appraisal 138. Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over (2008)[4].

AWMSG has previously issued a recommendation for the use of fluticasone furoate/vilanterol (as trifenatate) (Relvar® Ellipta®)[14].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company's submission includes two replicate phase III studies (205.416 and 205.417) comparing the efficacy of tiotropium versus placebo as an add-on treatment to patients whose asthma was inadequately controlled by a combination of a high-dose ICS with a LABA.

3.1 Studies 205.416 and 205.417

Studies 205.416 (n = 428) and 205.417 (n = 423) were 48-week, international, multicentre, randomised, double-blind, parallel-group, replicate studies. Tiotropium 2.5 micrograms (two inhalations daily given at the same time) using the Respimat® inhaler was evaluated versus placebo as an add-on treatment to usual care (ICS plus LABA maintenance medicines) for patients (aged 18–75 years) with asthma who had ≥ one severe exacerbation in the previous year[1,15]. Patients had to be receiving ≥ 800 micrograms of budesonide (or an equivalent ICS) plus a LABA to be eligible for inclusion in the study. Patients were allowed to continue their current concomitant medicines including oral corticosteroids, LTRAs, theophyllines and anti-IgE antibodies. All patients were allowed open-label salbutamol or albuterol as rescue medication during the studies. At screening, patients were required to have persistent airflow limitation, defined as a post-bronchodilator FEV_1, of ≤ 80% predicted FEV_1 (see Glossary) and ≤ 70% of forced vital capacity (FVC: see Glossary) 30 minutes after inhalation of four puffs of 100 micrograms of salbutamol or 90 micrograms of albuterol. Eligible patients received four weeks of screening before being randomised 1:1 to receive tiotropium or placebo. Patients had a mean baseline FEV_1 of 62% of the predicted value.

Primary endpoints included the change from baseline to 24 weeks in peak FEV_1 (measured within three hours of administering the maintenance treatments and study medicines) and the change from baseline in trough FEV_1 (pre-dose FEV_1 measured ten minutes before study medicine administration during maintenance therapy). Tiotropium was statistically superior versus placebo for peak and trough FEV_1 response at week 24 in both studies (see Table 1). Results from the two studies were pooled to provide sufficient statistical power to derive a further primary endpoint, the time to first severe exacerbation for patients in the two arms. Severe exacerbation was defined as a deterioration of asthma, necessitating initiation or at least a doubling of systemic corticosteroids for ≥ three days. The addition of tiotropium increased the time to first severe exacerbation by 56 days (282 days versus 226 days, representing the time until at least 25% of the patients had a first severe exacerbation), with a corresponding 21% decrease in the risk of a severe exacerbation (hazard ratio 0.79, 95% confidence interval: 0.61 to 1.00, p = 0.03)[1,15]. Less than 50% of patients had a severe exacerbation; therefore, the median time to first severe exacerbation could not be calculated[15].

The secondary endpoints: peak FEV_1 measurements at 4, 8, 16, 32, 40 and 48 weeks; peak and trough FVC at 24 and 48 weeks; and morning and evening peak expiratory flow at 24 and 48 weeks; were numerically higher for tiotropium-treated patients compared with those receiving placebo[1,15]. Further secondary endpoints included the Asthma Control Questionnaire (ACQ-7; see Glossary) score and patient-reported Asthma Quality of Life Questionnaire (AQLQ; see Glossary) score. Mean differences in ACQ-7 and AQLQ scores were significantly improved versus placebo at most time points in study 205.417 but not in study 205.416. The endpoints of number of asthma symptom-free days and rescue medication use, measured at both 24 weeks and 48 weeks, were not significantly different between the tiotropium and placebo arms[1,15].

Table 1. Results of studies 205.416 and 205.417[1,15]

	Study 205.416 (n = 428)		Study 205.417 (n = 423)	
	Mean treatment difference between tiotropium and placebo* (95% CI)	**p-value**	**Mean treatment difference between tiotropium and placebo* (95% CI)**	**p-value**
Co-primary endpoints				
Peak FEV_1 at 24 weeks (0–3 hours)	86 ml (20 to 152 ml)	< 0.05	154 ml (91 to 217 ml)	< 0.001
Trough FEV_1 at 24 weeks	88 ml (27 to 149 ml)	< 0.01	111 ml (53 to 169 ml)	< 0.001
Secondary endpoints†				
Peak FEV_1 at 48 weeks (0–3 hours)	73 ml (5 to 140 ml)	< 0.05	152 ml (87 to 217 ml)	< 0.001
Trough FEV_1 at 48 weeks	42 ml (−21 to 104 ml)	Not reported	92 ml (32 to 151 ml)	< 0.01

*mean change from baseline, adjusted for treatment, centre, visit, baseline value, and interactions between treatment and visit and between baseline value and visit. Tiotropium and placebo were added to usual care (ICS + LABA).
†secondary endpoints were determined for a slightly smaller number of patients, i.e. for 417 patients in study 205.416, and for 403 patients (peak FEV_1) and 402 patients (trough FEV_1) in study 205.417.
CI: confidence interval; FEV_1: forced expiratory volume in one second; ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; ml = millilitre; n: number of patients.

3.2 Comparative safety

The number of treatment-related adverse events in studies 205.416 and 205.417 were similar in the tiotropium and placebo arms (26 patients [5.7%] versus 21 patients [4.6%])[1,15]. Serious adverse events were reported for 37 patients (8.1%) in the tiotropium arm and 40 patients (8.8%) in the placebo arm. Three events in the tiotropium arm were considered to be life-threatening: two patients had asthma exacerbations and fully recovered, and one patient was admitted to hospital for cerebral infarction[1,15]. The most frequent serious adverse events by system organ class in either arm were respiratory, thoracic and mediastinal disorders, which occurred for 20 patients (4.4%) in the tiotropium arm and for 22 patients (4.8%) in the placebo arm[1,15].

3.3 AWTTC critique

- The addition of tiotropium significantly reduced severe asthma exacerbations and provided statistically significant but relatively small (< 10%) improvements in FEV_1. These FEV_1 improvements were seen despite patients already being on at least a high dose ICS/LABA regimen, and a proportion of patients were also on other add-on therapies (maintenance oral corticosteroids 5.3%, omalizumab 3.9%, theophyllines 16.7%, LTRAs 22.3%)[15].
- The BTS/SIGN 2016 guideline recommends tiotropium as one of four additional options which can be used[11]. In their submission, the company compared tiotropium plus usual care against usual care alone[1]; the submission does not include comparison with other treatment options, which may be added to treatment at the additional add-on therapy or high-dose therapy stage. The company outlined that the lack of evidence available for other treatment options meant it was unfeasible to make a robust comparison with tiotropium of the clinical and cost-effectiveness of the other treatment options.
- Welsh clinical experts contacted by the All Wales Therapeutics and Toxicology Centre (AWTTC) commented that there are very limited effective treatment options at the later stages of asthma treatment, and that tiotropium is currently used as a treatment option for asthmatics at the add-on therapy stage of treatment. They have expressed strong support for tiotropium to be available for this indication.
- The BTS/SIGN guideline recognises that there are few clinical studies at the high-dose therapies stage, and recommendations are largely based on extrapolation from trials of add-on therapy to ICS alone[11].
- The potential for side effects is greater with theophyllines and SR beta2-agonist tablets than for tiotropium[11].
- In a review of randomised control trials (RCTs) reported in the BTS/SIGN guideline, adults taking tiotropium in addition to ICS plus LABA demonstrated fewer asthma exacerbations (although results were inconclusive), improved lung function, and some benefits relating to asthma control, compared to patients taking ICS plus LABA[11].
- There was a larger placebo response in study 205.416 compared to study 205.417, and an inconsistency between the results in both studies for the change in peak FEV_1 at 24 weeks (0–3 hours). Both studies recruited patients with similar patient baseline characteristics, and the authors of the paper were unable to provide a rationale for the differences noted[15].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company's submission describes a cost-utility analysis (CUA) of tiotropium (Spiriva® Respimat®) 2.5 micrograms inhalation solution, as an add-on bronchodilator to usual care, compared to usual care alone (ICS plus LABA therapy)[1]: in adults with uncontrolled asthma, broadly reflecting the stage when there is the addition of add-on therapies to treatment in the BTS/SIGN guideline[1,11].

The analysis is based on a lifetime Markov model consisting of three asthma control states and three exacerbation-related health states. The asthma control states are defined by ACQ-7 scores collected in the two phase III studies (see Section 3.0). Optimal asthma control is defined as an ACQ-7 score < 1.0, acceptable asthma control as a score ≥ 1.0 to < 1.5, and uncontrolled asthma as a score ≥ 1.5. Exacerbations are defined in the phase III studies, and are categorised as non-severe, severe (requiring initiation or doubling of the existing dose of systemic corticosteroids for at least three days) without hospitalisation, and severe with hospitalisation[1]. Adverse events are excluded on the basis they did not differ significantly between tiotropium and placebo, and as no deaths were recorded in the phase III studies, the base case analysis assumes no asthma-related mortality occurs; age-specific mortality is assumed based on UK life tables. Incorporation of mortality associated with exacerbations is explored in a scenario analysis, using a published database study of asthma mortality following hospital admission[16].

All patients enter the model in the uncontrolled health state. Probabilities of transitioning to other asthma control states are derived from the pooled phase III study populations with complete ACQ-7 score data. As ACQ-7 scores were collected only at study-specified visits, weekly ACQ-7 scores have been imputed by assuming patients' previous ACQ-7 scores were constant in each week until the next study visit. ACQ-7 score was measured unless an exacerbation occurred, in which case the ACQ-7 score from the next study visit was assumed once the exacerbation ended. Transition probabilities in the first eight weeks reflect an early response phase, with ACQ-7 scores from the last 40 weeks of the studies used to extrapolate effectiveness over the remainder of the lifetime horizon. In contrast, the probabilities of experiencing exacerbations are assumed constant over time based on exacerbation rates observed throughout the phase III study durations.

Medicine acquisition costs for usual care are based on an average of budesonide 800 micrograms/formoterol 24 micrograms per day (Symbicort® 400/12 Turbohaler® inhalation powder) and salmeterol 100 micrograms/fluticasone propionate 500 micrograms per day (Seretide® 25/125 Evohaler®). Tiotropium acquisition cost is based on the licensed dose of Spiriva® Respimat®. Other baseline treatment costs are assumed equal between treatment arms. Use of rescue medication (salbutamol) is assumed to be constantly marginally lower for tiotropium compared with usual care (2.26 puffs versus 2.52 puffs per day), irrespective of health state. In contrast, co-medication required during exacerbations, laboratory tests and procedures, and outpatient or home visits are incorporated and differ by health state based on a survey of 15 UK healthcare professionals experienced in the management of people with asthma. Other direct healthcare resource uses, including hospitalisations, and accident and emergency department visits, are derived from the phase III studies[1]. Published unit costs, inflated to 2016/17 prices where appropriate, have been applied.

The addition of tiotropium to usual care in the phase III studies did not result in a significant difference in quality of life scores measured with the EQ-5D instrument; therefore, average utility scores for each asthma control health state are based on pooled EQ-5D scores from both arms at the last visit of the phase III studies[1]. Utility values for severe exacerbations are based on a published UK study[17], and in the absence of utility values for non-severe

exacerbations, a value mid-way between those for uncontrolled asthma and non-hospitalised severe exacerbations is assumed[1]. Costs and outcomes beyond one year are discounted at 3.5% per annum.

4.1.2 Results

The results of the base case analysis are presented in Table 2. Over a discounted lifetime horizon of analysis (17.98 years as modelled), the addition of tiotropium to usual care resulted in an incremental cost per quality-adjusted life-year (QALY) gained of £13,341, based on an increase in total costs of £2,877 and a gain of 0.22 QALYs.

Patients remain for the largest part of the modelled time horizon in the uncontrolled asthma state, both with or without the addition of tiotropium to usual care. The bulk of costs and QALYs are therefore accrued in the uncontrolled asthma state. The overall QALY gains with addition of tiotropium arise from the reduced time patients are modelled to spend in the uncontrolled asthma state, and in the non-severe and severe exacerbation without hospitalisation states, which increases the amount of time patients spend in the optimal and acceptable asthma control state with improved quality of life compared with usual care alone.

Table 2. Results of the base case analysis

	Tiotropium plus usual care	Usual care	Difference
Total costs	¶¶	¶¶	**£2,877**
Total life-years	17.98	17.98	**0**
Total QALYs	14.49	14.28	**0.22**
ICER (£/QALY gained)	**£13,341**		

¶¶: commercial in confidence figures removed
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

In a range of one-way sensitivity analyses around health state resource use estimates and utility values, exploring variation in inputs in the range of their 95% confidence or ±10%, the majority of incremental cost-effectiveness ratio (ICER) estimates remained in the range £10,000–15,000 per QALY gained. When the cost for optimal asthma control was increased to £46.41 (base case cost £7.94), the ICER was £21,607; this was the only analysis which resulted in an ICER above £20,000 per QALY. The model outputs were most sensitive to the estimated resource use associated with uncontrolled asthma, the assumed discount rate for costs and outcomes, and the estimated resource use associated with the optimal asthma control health state (Table 3).

Uncertainty in efficacy variables was included in probabilistic sensitivity analysis, which involved random sampling of transition probabilities simultaneously with other parameter values. The probability of the addition of tiotropium to usual care resulting in an ICER below £20,000 per QALY was 69.3%, and below £30,000 per QALY was 83.1%. Tiotropium was dominant (more effective/less costly) in 2.5% of the simulations, was more effective and more costly in 96.2% of simulations, and tiotropium was dominated in 1.3% of simulations.

Scenario analyses explored incorporation of mortality risk in patients hospitalised with severe exacerbations, a 20% reduction in selected utility values, the use of transition probabilities derived from weeks 47–48 of the clinical studies for extrapolation of long-term effects, and incorporation of work productivity losses in the model to reflect a societal perspective. Those having a material impact on the ICER are presented in Table 3.

Table 3. Results of scenario analyses

Scenarios	ICER	Plausibility
Inclusion of mortality risk associated with severe exacerbations requiring hospitalisation	£11,041	ICER reduced compared with base case. The company suggests this analysis is the most appropriate because exclusion of mortality from the base case is overly conservative. The phase III studies were not powered for hospitalisations, no significant difference in rates of hospitalisations for severe exacerbations between tiotropium and usual care alone were found, and no asthma deaths over 48 weeks were observed[1]; this analysis would appear subject to considerable uncertainty.
Reducing the model time horizon from lifetime to 20 years	£13,436	No explanation was given for reducing the time horizon to 20 years.
A 20% difference in the utility benefit provided by tiotropium. Acceptable asthma control and severe exacerbations without hospitalisations stay the same as in the base case	£14,777	This scenario was to investigate a more conservative set of assumptions regarding the utility of patients being in certain health states. The values were not based on clinical trial data; therefore, it is not possible to determine the plausibility of the values tested.
A reduction of 20% in the utility benefit provided by tiotropium. Uncontrolled asthma and severe exacerbations with hospitalisations stay the same as in the base case	£12,670	
Reducing the model time horizon from lifetime to 20 years and a reduction in the utility benefit provided by tiotropium: utility values for acceptable asthma control and severe exacerbations without hospitalisation stay the same as in the base case	£14,879	These scenarios were a combination of a 20 year time horizon and conservative assumptions of the utilities. These changes were not based on clinical trial data and so the plausibility of the values cannot be determined from the information presented.
Reducing the model time horizon from lifetime to 20 years and a reduction in the utility benefit provided by tiotropium: utility values for uncontrolled asthma control and severe exacerbations with hospitalisation stay the same as in the base case	£12,762	
Long-term transition probabilities based on trial data from weeks 47–48	£1,159	The company notes this analysis should be viewed with extreme caution, due to the scarcity of data to reliably inform estimation of transition probabilities at this stage of the clinical study.
Incorporation of indirect costs of work days lost due to asthma	£3,624	The base case appropriately adopted an NHS and Personal Social Services perspective. Work days lost due to asthma for each health state in this scenario are based on estimates from a survey of 15 healthcare professionals, rather than observed data, and are subject to uncertainty.
ICER: incremental cost-effectiveness ratio		

4.1.3 AWTTC critique

The company's analysis considers addition of tiotropium to usual care only; no other agents recommended as add-on treatments in the BTS/SIGN guideline are considered as comparators, although it should be noted that there is a paucity of evidence for their use in this patient group at this stage[11].

The company's model uses post hoc subgroup analyses of study data to define health states and model probabilities of transitioning between health states, which are subject to uncertainty. These have been extrapolated over a lifetime horizon, assuming long-term stable treatment effects. The model effectively assumes all patients remain at the stage of adding in additional treatment and above of the BTS/SIGN guideline, and predicts shifts towards greater asthma control and improved quality of life with the addition of tiotropium over the lifetime horizon, although the study data did not consistently observe this with the addition of tiotropium to usual care. Collectively, the base case analysis appears subject to considerable uncertainty, reflected in the results of the probabilistic sensitivity analysis. It is not clear if the analysis would reflect the cost-effectiveness in all patients or those with persistent airflow limitations.

Key strengths of the economic evidence include:

- The model employs direct comparative efficacy data, quality of life and resource-use data, where available from the key clinical studies. Expert opinion has been solicited to inform parameter values where necessary.
- A wide range of sensitivity analyses have been conducted to explore uncertainty in parameter values, and alternative scenario analyses are provided.

Key limitations and uncertainties in the economic evidence include:

- Tiotropium plus usual care is compared against usual care alone. The BTS/SIGN guideline recommends the following add-on therapies as alternatives to tiotropium: LTRA, SR theophylline or a beta2-agonist[11]. At this stage in treatment, increasing the doses of previously prescribed therapies is also recommended. No alternatives are included in the model, which introduces uncertainty; however, the company provides the rationale that the evidence for these other add-on therapies at this treatment stage is lacking, and evidence for their use is largely based on extrapolation from historical trials where their efficacy was examined as add-on therapy to ICS alone[1].
- It is unclear whether the study results and, hence, the economic evidence could be generalised to all people at the additional add-on therapy stage of the BTS/SIGN treatment guideline. It is implicitly assumed that people remain at this stage and above throughout the lifetime horizon.
- The modelled efficacy is based on post hoc subgroup analyses, which have the potential to introduce numeric differences between treatments that are due to chance. As treatment effects are assumed stable over a lifetime, these differences are subsequently propagated over the lifetime horizon of analysis. On the basis of these analyses, the model predicts addition of tiotropium will increase the proportion of time people spend in optimal and acceptable controlled asthma states, which are modelled to be experienced with improved quality of life, over a lifetime horizon. However, improvements in asthma control assessed by various measures were not consistent in the phase III study data[18], which observed that: there were no statistically significant improvements over placebo in the number of asthma symptom-free days or the use of rescue medication (pre-specified study endpoints); improvements in asthma symptom control and asthma-specific quality of life scores from baseline were seen in both the tiotropium and placebo arms.
- There was a large placebo effect observed in the 205.416 study, and the results for FEV_1 response and quality of life endpoints were not significant. However, significant differences were seen in the 205.417 study. The differences in treatment effect are assumed to remain over the lifetime of the model. However, the company has tested the time horizon of the model, and therefore the data extrapolation, in the sensitivity analyses. Also, the company has justified the base case, as the model becomes stable after 104 weeks, and the proportion of patients in each health state remains close to that seen in the clinical studies, except for deaths. The proportion of patients in the hospitalised exacerbation state is slightly overestimated for the tiotropium arm; the model did not capture potential benefits of tiotropium on the length of exacerbations.

- The evidence for severe exacerbations requiring hospitalisation is based on pooled analysis, and it is not possible to tell if it is statistically significant[1]. Given this, the uncertainty in the assumption of people remaining at the additional add-on therapy stage, and the uncertainty in the differential treatment effects that are extrapolated over the long term, a shorter time horizon of analysis may be appropriate, and would increase the ICER estimates. The impact of the time horizon has been tested in the sensitivity analyses; a shorter time horizon of 20 years resulted in an ICER of £13,436 per QALY and when a time horizon of 5 years was used, the ICER increased to £14,287 per QALY.
- The company suggests the scenario analysis incorporating a mortality risk for severe exacerbations requiring hospitalisation is the most appropriate, as exclusion of mortality from the base case analysis is conservative. However, there is no evidence to support a differential effect of tiotropium on hospitalisation due to severe exacerbations or mortality, and this scenario analysis is subject to the same uncertainties as the base case analysis regarding extrapolation of differential treatment effects over a lifetime horizon. The company justified the inclusion of a mortality benefit as tiotropium has been shown to reduce the risk of exacerbations, and therefore this scenario has assumed that there is a consequent reduction of severe exacerbations that require hospitalisation.

4.2 Review of published evidence on cost-effectiveness

A CUA of tiotropium as an add-on to usual care compared with usual care alone, conducted by the company from the perspective of the UK NHS, has been published[19]. This is structurally the same model as submitted to AWMSG by the company, but uses ACQ-6 scores. Earlier resource use estimates and costs from 2012 do not reflect the revised medicine cost for tiotropium. Over a lifetime horizon, the incremental cost per QALY gained for the addition of tiotropium to usual care was estimated to be £21,906.

Three conference abstracts were identified as relevant to this review, one in a Spanish setting[20], one in Poland[21] and one in the United States[22]. The Spanish and Polish analyses compared tiotropium to usual care, and the United States analysis compared tiotropium to omalizumab. In all three, tiotropium was found to be cost-effective compared to the alternative. However, abstracts do not present enough information to fully understand the analysis and methods, and the results are not directly applicable to the Welsh healthcare setting.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on Quality and Outcomes Framework (QOF) register data, the company estimates there will be between 177,493 and 250,384 adults with asthma eligible for treatment in Wales, with an average yearly increase of 0.83%[5]. It is assumed that 79.74% of patients are eligible for treatment and 20.02% of patients with uncontrolled asthma are currently treated with high-dose ICS plus LABA. The company forecasts for the uptake of tiotropium in these patients is commercial in confidence.

Based on the rates of severe and hospitalised exacerbations observed in the phase III studies data[15], unit costs of asthma hospitalisations, GP visits and accident and emergency visits, the company estimates the annual cost savings associated with exacerbations avoided per patient treated with tiotropium to be £23.02**.**

5.1.2 Results

The company estimates the net budget impact in Wales in each of the next five years, taking account of the additional acquisition costs of tiotropium and the cost savings from severe exacerbations avoided, as in Table 4. The total budget impact for 5 years is commercial in confidence.

Table 4. Company-reported costs associated with use of tiotropium for the treatment of asthma

	Year 1 (2017)	Year 2 (2018)	Year 3 (2019)	Year 4 (2020)	Year 5 (2021)
Number of eligible asthma patients in Wales	224,446	226,318	228,206	230,109	232,028
Number of eligible patients (uncontrolled asthma)	35,831	36,129	36,431	36,735	37,041
Uptake (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Treated patients	¶¶	¶¶	¶¶	¶¶	¶¶
Net costs					
Medication costs	£279.83	£279.83	£279.83	£279.83	£279.83
Net costs per patient	£256.81	£256.81	£256.81	£256.81	£256.81
Drug acquisition	£279.83	£279.83	£279.83	£279.83	£279.83
Exacerbation-associated costs	-£23.02	-£23.02	-£23.02	-£23.02	-£23.02
Overall net cost	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶: commercial in confidence figures removed					

If the market uptake assumptions are increased by 50%, then the budget impact for 5 years increases to [commercial in confidence data removed]. If the market uptake assumptions are decreased by 50%, then the budget impact decreases to [commercial in confidence data removed] over 5 years. If there is no benefit from reduced exacerbation-associated costs, then the budget impact over 5 years will be [commercial in confidence data removed]. If the total number of adults in Wales who would be considered eligible for therapy was the upper end of the estimation by clinical experts (17,000 patients), then the budget impact will be [commercial in confidence data removed].

5.1.3 AWTTC critique

- The company has adopted a pragmatic approach to estimate the number of patients eligible for treatment with tiotropium.

5.2 Comparative unit costs

Table 5. Examples of medicine acquisition costs for uncontrolled asthma

Regimens	Example doses	Approximate costs per patient (per year)
Tiotropium 2.5 micrograms[§] (Spiriva® Respimat®)	2 inhalations once daily £23.00 for 60 sprays	£279.83
Leukotriene receptor antagonists		
Montelukast[¶] (Non-proprietary)	10 mg once daily in the evening £1.71 for 28 tablets	£22.29
Zafirlukast (Accolate®)[§]	20 mg twice daily £17.75 for 56 tablets	£231.38
Slow release theophylline		
Nuelin SA® 250 mg[§]	250–500 mg twice daily £8.92 for 60 tablets	£109 to £217
Slo-Phyllin® 250 mg[§]	250–500 mg twice daily £4.34 for 56 capsules	£57 to £113
Uniphyllin Continus®[§]	200–400 mg every 12 hours £2.96 for 56 tablets, 200 mg £5.65 for 56 tablets, 400 mg	£39 to £74
Not all regimens may be licensed for use in this patient population. See relevant SPC. [§]Costs are based on MIMS list prices[23]. [¶]Costs are based on the NHS drug tariff[24]. Costs of administration are not included. This table does not imply therapeutic equivalence of drugs or the stated doses.		
MIMS: Monthly Index of Medical Specialties; SPC: Summary of Product Characteristics		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, tiotropium (Spiriva® Respimat®) may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 6 June 2017 and 8 June 2017.
Date range of evidence search: No dates limits were applied to database searches.

GLOSSARY

Asthma Control Questionnaire 7 (ACQ-7)
The Asthma Control Questionnaire 7 (ACQ-7) consists of seven questions relating to the top five scoring symptoms, FEV_1% predicted and daily rescue bronchodilator use. Clinical staff score the FEV_1% predicted. The answers to the seven questions are equally weighted and the ACQ score is recorded as the mean of the answers, each scored on a scale of 0 (no impairment) to 6 (maximum impairment). A change in score of 0.5 points is the smallest that is considered clinically important[25].

Asthma Quality of Life Questionnaire (AQLQ)
The Asthma Quality of Life Questionnaire (AQLQ) was developed to measure the functional problems (physical, emotional, social and occupational) that are most troublesome to adults with asthma. The questionnaire consists of 32 questions in four domains (symptoms, activity limitation, emotional function and environmental stimuli). Patients are asked to consider their asthma-related symptoms and limitations during the preceding two weeks. Each question is scored on a scale of 1 (severely impaired) to 7 (no impairment). The overall AQLQ score is the mean of all 32 responses. A change in score of 0.5 points is the smallest that is considered clinically important[26].

Forced expired volume in one second (FEV_1)
The forced expired volume in one second is the volume of air that can be expelled from maximum inspiration in the first second[4].

Forced vital capacity (FVC)
The volume of lungs from full inspiration to forced maximal expiration, expressed as a percentage of the predicted normal for a person. FVC is reduced in restrictive disease and also in obstructive disease if air-trapping accurs[27].

Peak Expiratory Flow (PEF)
A measurement of how fast a person can exhale, using a peak flow monitor[28]. This was measured within three hours of administration of the maintenance and study treatments[15].

Percentage Predicted FEV_1
A percentage of the predicted FEV_1 for a person of the same height, sex and age without diagnosed asthma[4].

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