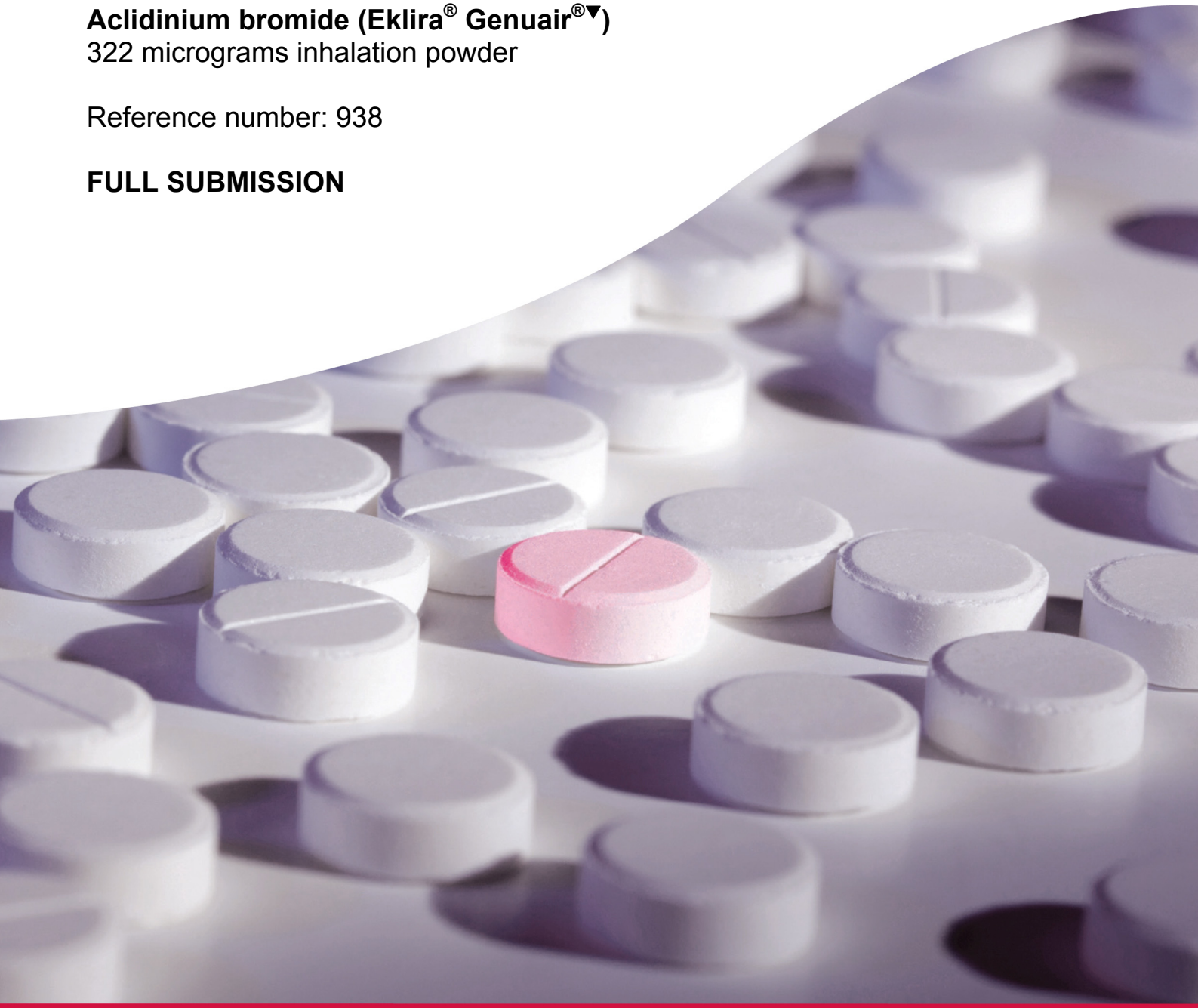
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Aclidinium bromide (Eklira® Genuair®▼)
322 micrograms inhalation powder

Reference number: 938

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Aclinidium bromide (Eklira® Genuair®▼) 322 micrograms inhalation powder

This assessment report is based on evidence submitted by Almirall Ltd on 19 October 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Aclidinium bromide (Eklira® Genuair®▼) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease[2].
Dosing	The recommended dose is one inhalation of 322 micrograms aclidinium twice daily. Each delivered dose (the dose leaving the mouthpiece) contains 375 micrograms aclidinium bromide, equivalent to 322 micrograms of aclidinium[2].
Marketing authorisation date	20 July 2012[2]
UK launch date	1 August 2012[1]

2.0 DECISION CONTEXT

2.1 Background

Chronic obstructive pulmonary disease (COPD) is the term used to encompass a number of lung conditions, including chronic bronchitis, emphysema, chronic obstructive airway disease and chronic airflow limitation[3]. COPD is characterised by deterioration of lung function due to progressive airflow obstruction that is not fully reversible (see Glossary)[3–5]. Typical symptoms of COPD include persistent and progressive breathlessness, a chronic productive cough and limited exercise capacity[3]. The development of COPD is accepted to be linked to exposure to cigarette smoke, chemicals and occupational dusts[4,6]. It is estimated that three million people have COPD in the UK, of which approximately 900,000 are diagnosed[5]. As of September 2012, there are 66,951 patients diagnosed with COPD in Wales[5]. COPD prevalence increases with age and is rare in people under the age of 35 years[3].

COPD treatments aim to reduce symptoms, reduce the frequency and severity of exacerbations, improve health status and increase exercise tolerance. Bronchodilators are central to the pharmacological management of COPD symptoms. Current global guidelines state that inhaled therapy is preferred and is given on either an as-needed basis (short-acting) or a regular basis (long-acting, maintenance therapy) to prevent or reduce symptoms[6].

Typically, long-acting beta$_2$-agonists (LABA) and long-acting muscarinic receptor antagonists (LAMA) are used for moderate to severe COPD[6]. Inhaled corticosteroid is also recommended as additional therapy for severe COPD[5,6]. Aclidinium bromide (Eklira® Genuair®▼) is an inhaled LAMA, or anticholinergic, which has a strong affinity and selectivity for all muscarinic receptor subtypes (M1–M5) and a kinetic selectivity for

the M3 receptors. The M3 receptors mediate contraction of airway smooth muscle; therefore, by antagonising these receptors with inhaled aclidinium bromide, bronchodilation may be induced[2,4].

2.2 Comparators

The applicant company, in agreement with the All Wales Therapeutics and Toxicology Centre (AWTTC), have identified the inhaled LAMA tiotropium bromide monohydrate (Spiriva®) as the most appropriate comparator.

2.3 Guidance and related advice

- National Institute for Health and Care Excellence (NICE). Evidence summaries: new medicines (ESNM) 8. Chronic obstructive pulmonary disease: aclidinium bromide (2013)[7].
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease (2011)[6].
- NICE. Clinical Guideline 101: Chronic obstructive pulmonary disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update) (2010)[5].

The All Wales Medicines Strategy Group (AWMSG) considered in March 2013:

- Glycopyrronium bromide (Seebri® Breezhaler®▼) as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD[8].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included details for two pivotal placebo-controlled phase III clinical trials, ATTAIN (LAS-MD-34) and ACCORD I (LAS-MD-33), which described the efficacy and safety of aclidinium bromide for the treatment of moderate to severe COPD. Due to the similarities in study design, ATTAIN and ACCORD I are described together below. Two doses of aclidinium bromide (200 micrograms twice-daily and 400 micrograms twice-daily) were investigated in these studies; however the focus of this submission will be on the aclidinium bromide 400 micrograms twice-daily dose (corresponding to the licensed delivered dose of 322 micrograms twice-daily aclidinium) and so results pertaining to the aclidinium bromide 200 micrograms twice-daily dose will not be discussed further. Additional information provided as academic/commercial in confidence.

To enable a comparison of the clinical effectiveness of aclidinium bromide and tiotropium bromide monohydrate, the company submission included results from a six-week phase IIIb trial (LAS-MD-39), which compared aclidinium bromide 400 micrograms twice-daily to both tiotropium bromide monohydrate 18 micrograms once-daily and placebo. In the absence of substantial head-to-head data, the company also performed an indirect comparison of aclidinium bromide and tiotropium bromide monohydrate[1].

Two further phase III studies, LAS-MD-35 and LAS-MD-36, evaluated longer-term safety (52 weeks) of aclidinium bromide, as well as some efficacy outcomes; however limited data have been provided.

3.1 Placebo-controlled studies: ATTAIN and ACCORD I

ATTAIN and ACCORD I were multicentre, randomised, double-blind, placebo-controlled, parallel group phase III trials designed to assess the efficacy and safety of aclidinium bromide in patients (≥ 40 years, who were current or former cigarette smokers) with a diagnosis of stable moderate to severe COPD, defined according to GOLD guidelines[6]. Patients with clinically significant cardiovascular

conditions were excluded from the trials. Patients were randomised 1:1:1 to receive aclidinium bromide 200 micrograms, aclidinium bromide 400 micrograms (equivalent to the licensed dose of 322 micrograms) or placebo twice-daily, administered using a multidose dry powder inhaler (Genuair®). The ATTAIN study consisted of a two week run-in period, a 24-week treatment period and a two-week follow-up period. The ACCORD I study structure was the same with the exception of the treatment period, which was shorter at 12 weeks[1,4,9,10].

The primary endpoint was the change from baseline in morning pre-dose (trough) forced expired volume in one second (FEV_1; see Glossary) at week 24 and week 12 for ATTAIN and ACCORD I, respectively. For ATTAIN, a statistically significantly improvement was observed with aclidinium bromide 400 micrograms twice-daily over placebo (55 ml versus −73 ml; treatment difference 128 ml; 95% confidence interval [CI]: 85, 170; p < 0.0001). For ACCORD I, a statistically significant improvement was demonstrated for aclidinium bromide 400 micrograms twice-daily over placebo (99 ml versus −25 ml; treatment difference 124 ml; 95% CI: 83, 164; p < 0.0001). These results were supported by statistically significant improvements in key secondary endpoints, which included breathlessness on the transition dyspnoea index (TDI) at 26 weeks and health-related quality of life according to the St. George's Respiratory Questionnaire (SGRQ) (see Table 1)[1,4,9,10].

Table 1. Results of the ATTAIN and ACCORD I studies[1,4,9,10]

	Aclidinium bromide 400 micrograms	Placebo	Aclidinium bromide versus placebo
ATTAIN	**n = 269**	**n = 273**	
Mean change in trough FEV_1 at 24 weeks (ml)	55	−73	128 p < 0.0001
Mean change in TDI focal score at 24 weeks	1.9	0.9	1.0 p = 0.0006
Mean change in SGRQ total score at 24 weeks	−7.4	−2.8	−4.6 p < 0.0001
ACCORD I	**n = 190**	**n = 186**	
Mean change in trough FEV_1 at 12 weeks (ml)	99	−25	124 P< 0.0001
* Result did not reach the minimal clinically important difference of 4 points FEV1: forced expired volume in one second; TDI: transition dyspnoea index; SGRQ: St. George's Respiratory Questionnaire			

Additional information provided as academic/commercial in confidence.

3.2 Comparative efficacy

3.2.1 LAS-MD-39

LAS-MD-39 was a randomised, multicentre, double-blind, double-dummy placebo- and active comparator-controlled, parallel phase IIIb study, which compared the efficacy of aclidinium bromide 400 micrograms twice-daily, tiotropium bromide monohydrate 18 micrograms once-daily and placebo in patients (≥ 40 years) with a diagnosis of stable moderate to severe COPD, defined according to GOLD guidelines[6]. Patients (n = 414) were randomised to receive aclidinium bromide 400 micrograms twice-daily tiotropium bromide monohydrate 18 micrograms once-daily or placebo[11]. Additional information provided as academic/commercial in confidence.

The primary efficacy endpoint was the change from baseline in normalised FEV_1 area under the curve over the 24-hour period immediately after morning treatment administration, following six weeks of treatment. A statistically significant improvement was demonstrated for aclidinium bromide 400 micrograms twice-daily versus placebo (150 ml; p < 0.0001). A similar improvement in FEV_1 was seen for tiotropium bromide monohydrate 18 micrograms once-daily versus placebo (140 ml; p < 0.0001). A

numerically greater, but not statistically significant, increase in change from baseline in FEV_1 was shown for aclidinium bromide compared to tiotropium bromide monohydrate (10 ml; $p > 0.05$)[11].

3.2.2 Indirect comparison

Additional information provided as academic/commercial in confidence.

3.2.3 Supportive studies

LAS-MD-36 and LAS-MD-35 were randomised, double-blind, parallel group phase III studies, which were primarily designed to investigate the safety of aclidinium bromide in patients with COPD at 52 weeks. LAS-MD-36 was an extension study for subjects that had participated in ACCORD I; patients that had previously received aclidinium bromide in ACCORD I continued treatment with aclidinium bromide at the same dose (400 micrograms: n = 91; 200 micrograms; n = 76), while patients that had previously received placebo were randomised to aclidinium bromide 400 micrograms twice-daily (n = 41) or 200 micrograms twice-daily (n = 38). In study LAS-MD-35, patients were randomised to aclidinium bromide 400 micrograms twice-daily (n = 290) or 200 micrograms twice-daily (n = 310) at study commencement[4].

The primary efficacy endpoint was the change from baseline in morning pre-dose (trough) FEV_1 at week 52 (for study LAS-MD-35) and at week 64 (for study LAS-MD-36). In both studies, an improvement in trough FEV_1 was demonstrated and maintained in patients receiving aclidinium bromide 400 micrograms twice-daily[4].

3.3 Comparative safety

The comparative safety of aclidinium bromide 400 micrograms twice-daily versus tiotropium bromide monohydrate 18 micrograms once-daily was evaluated using an indirect comparison; however, the company state that a quantitative analysis of adverse events (AE) data was not appropriate due to inconsistencies in available data (e.g. the inclusion of worsening COPD symptoms as an AE) and low numbers of AEs reported in the placebo arm and have provided a qualitative analysis. The applicant company suggest that aclidinium bromide 400 mg twice-daily provides a comparable safety profile to tiotropium bromide monohydrate 18 mg once-daily, but may be associated with fewer anticholinergic AEs, for example, dry mouth was reported in 2.1% to 9.8% of patients in the tiotropium bromide monohydrate 18 micrograms once-daily studies; however, in the aclidinium bromide 400 micrograms twice-daily studies, dry mouth was reported in < 1% of patients (comparable to placebo)[1]. Serious AEs (SAEs) were also found to be comparable between groups (4.4% for the aclidinium bromide 400 micrograms twice-daily studies[4] versus 4.1%–6.8% in the tiotropium bromide monohydrate studies)[1]. Additional information provided as academic/commercial in confidence.

The company also provided a pooled safety analysis of the three phase III clinical trials, ATTAIN, ACCORD I and ACCORD II up to six months. Adverse events (AEs) were comparable between treatment and placebo groups; the most frequently occurring AEs included COPD exacerbations (11.8% for aclidinium bromide versus 15.6% for placebo), nasopharyngitis (5.5% for aclidinium bromide versus 3.9% for placebo) and headache (6.6% for aclidinium bromide versus 5.0% for placebo)[4]. The most frequent SAE was COPD exacerbation, which was reported at a lower incidence for aclidinium bromide 400 mg twice-daily group compared to placebo (1.6% versus 2.7%)[4]. Overall, including the longer-term safety studies, 9.7% of patients in the aclidinium bromide 400 mg twice-daily group discontinued due to AEs[4]. In total, 14 deaths were reported in the aclidinium bromide twice-daily studies (all studies in COPD patients); one of these deaths was thought to be related to the study medication[4].

3.4 AWTTC critique

- Results of the ATTAIN and ACCORD I studies show that aclidinium bromide demonstrated statistically significant improvements in the change from baseline FEV_1 compared to placebo. Both studies report changes in trough FEV_1 greater than 100 ml[9,10]. According to NICE CG101, a difference of 100 ml is considered to be clinically important[5].
- The pivotal studies outlined in the company submission provided efficacy data with clinical outcomes demonstrated at 12 and 24 weeks only[1]. However the two longer-term studies, LAS-MD-35 and LAS-MD-36, which were primarily safety studies, also demonstrated favourable efficacy outcomes, these were maintained for up to 52 and 64 weeks
- The applicant company have provided an indirect comparison of aclidinium bromide 400 micrograms twice-daily and tiotropium bromide monohydrate 18 micrograms once-daily as supportive evidence. The results were found to be comparable but with wide confidence intervals[1]. While an indirect comparison is a common approach to overcome the lack of direct comparative data, they have inherent limitations.
- Patients with cardiovascular conditions were excluded from the clinical trials included in the company submission. The European Medicines Agency (EMA) state that cardiovascular AEs need to be monitored further in the risk management plan and also in a post-authorisation safety study[4].
- Owing to sample size, only the ATTAIN study was sufficiently powered to detect treatment differences in SGRQ and TDI[9].
- Aclidinium bromide 400 micrograms is inhaled twice-daily, whereas tiotropium bromide monohydrate 18 micrograms is inhaled once-daily[1,12]; this could potentially influence adherence and patient preferences.
- The Genuair® inhaler device contains a one-month supply of aclidinium bromide and does not need to be refilled by the patient. The company report that this reduces potential error and device misuse[1]. The company have highlighted that, in direct comparative studies with the Handihaler® device (used to deliver tiotropium bromide monohydrate), the Genuair® inhaler device was mostly preferred by patients, and resulted in fewer critical use errors[1].
- The studies included in the company submission only refer to patients with moderate to severe COPD[1]. While no evidence for the use of aclidinium bromide in patients with mild or very severe COPD has been provided, in practice, a LAMA would be most typically used in patients with moderate to severe COPD[6].
- Glycopyrronium bromide is another LAMA that has recently been licensed as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD[13]; however no comparative data is available.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-minimisation analysis (CMA) of aclidinium bromide compared to tiotropium bromide monohydrate for the maintenance bronchodilator treatment of patients with COPD[1]. Aclidinium bromide is delivered twice-daily using a Genuair® multi-dose dry powder inhaler containing 60 doses of aclidinium bromide, and tiotropium bromide monohydrate is assumed to be delivered once daily using a HandiHaler® dry powder inhalation device, which disperses a single dose of tiotropium bromide monohydrate from a hard capsule.

The economic model presented by the company assumes the therapeutic equivalence of aclidinium bromide and tiotropium bromide monohydrate, based on results of network meta-analyses that indirectly compare lung function, breathlessness,

exacerbation rates and functional status observed in published placebo-controlled trials of aclidinium bromide and tiotropium bromide monohydrate. The CMA considers time horizons of one and five years, and incorporates acquisition costs only.

4.1.2 Results

Results of the base case analysis are summarised in Table 2, assuming each one-year supply of tiotropium bromide monohydrate is provided as one combination pack containing a HandiHaler® device and 30 capsules, and eleven 30-capsule refill packs. Assuming continuous treatment of patients with COPD, the company estimates that treatment with aclidinium bromide will save £60.17 per patient per year due to lower acquisition costs compared to tiotropium bromide monohydrate.

Table 2. Company-reported results of the base case CMA over a period of five years

	1 year	2 years	3 years	4 years	5 years
Aclidinium bromide 322 micrograms twice-daily	£343.20	£674.79	£995.18	£1,304.72	£1,603.80
Tiotropium bromide monohydrate 18 micrograms once-daily	£403.37	£793.10	£1,169.65	£1,533.47	£1,884.98
Difference	−£60.17	−£118.31	−£174.47	−£228.74	−£281.18
Costs were discounted at annual rate of 3.5% following year one					

Based on company-obtained prescribing data, tiotropium bromide monohydrate recipients in Wales are prescribed an average of three tiotropium bromide monohydrate combination packs per year, rather than one. In this scenario, the estimated cost saving due to the introduction of aclidinium bromide would increase to £62.91 per patient per year.

4.1.3 AWTTC critique

The reliability of the CMA presented by the company is dependent upon the extent to which aclidinium bromide is considered to have been demonstrated to be therapeutically equivalent to tiotropium bromide monohydrate[1]. In the absence of direct comparative data, the company has based its assumption of therapeutic equivalence of aclidinium bromide and tiotropium bromide monohydrate on indirect comparisons of placebo-controlled published studies, which were heterogeneous with respect to baseline disease status and concomitant medication. There were no statistically significant differences in lung function measures, exacerbation rates and quality of life estimates, but the CI range around relative exacerbation rates is relatively wide[1]. The CMA framework precludes exploration of the impact of this uncertainty and of consideration of other factors, such as patient preferences for administration regimens and drug delivery devices.

Strengths of the economic evidence include:

- In the absence of direct comparative data the company has undertaken a systematic literature review to identify studies for inclusion in adjusted indirect comparisons.
- A range of efficacy measures have been considered to explore the equivalence of aclidinium bromide and tiotropium bromide monohydrate, and sensitivity analyses have been conducted to explore the impact of some causes of heterogeneity among the studies.

Limitations of the economic evidence include:

- Studies included in network meta-analyses varied with respect to inclusion criteria, baseline characteristics and concomitant medication. Although

adjustment for some differences in study populations have been explored, results of the meta-analyses are characterised by wide credible intervals, and therefore are subject to uncertainty that may not be further explored in a CMA framework. This may be particularly relevant for clinically and economically important endpoints such as moderate to severe exacerbation rates, which were not statistically significantly improved compared with placebo in direct comparative trials, and were numerically (but not statistically significantly) higher than tiotropium bromide monohydrate in the network meta-analyses, including those that adjusted for some differences in trial participant baseline characteristics.

- The maximum follow up period for the aclidinium randomised controlled trials included in the network meta-analysis is 24 weeks.
- The CMA framework assumes therapeutic equivalence in all domains of health outcomes including effectiveness, AEs, adherence and preference. Any potential differences in preferences or adherence as a result of different device characteristics and administration regimens are not considered.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches did not identify any published studies on the cost-effectiveness of aclidinium bromide compared to tiotropium bromide monohydrate for the maintenance bronchodilator treatment of patients with COPD.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

According to the Quality and Outcomes Framework (QOF) disease register, there were 64,903 people with COPD in 2010–2011 in Wales[14]. Using a COPD prevalence rate of 2.05% for Wales and an incidence rate of 2% derived from a cross-sectional study of primary care patients in England[15], the company estimated that the number of patients receiving maintenance bronchodilator treatment will increase from 62,812 to 64,386 in five years[1]. Additional information provided as academic/commercial in confidence.

5.1.2 Results of company's budget impact analysis

The company-reported numbers of patients eligible for treatment with aclidinium bromide and the associated costs over the five-year period are summarised in Table 3. According to company estimates, treatment with aclidinium bromide would cost £343.20 per patient per year, while treatment with tiotropium bromide monohydrate would cost £403.37 per patient per year. The total cost of treating patients with aclidinium bromide will be £323,294 in year one rising to £2,209,865 in year five. Due to the anticipated displacement of tiotropium bromide monohydrate by aclidinium bromide, the company expects acquisition cost savings of £56,691 in year one rising to £387,413 in year five[1].

Table 3. Company-reported costs associated with the use of aclidinium bromide for the maintenance treatment of patients with COPD

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	62,812	63,430	63,747	64,066	64,386
Number of patients treated with LAMAs	31,406	31,715	31,874	32,033	32,193
Uptake	3%	7%	11%	16%	20%
Number of treated patients	942	2,220	3,506	5,125	6,439
Overall net cost	**−£56,691**	**−£133,581**	**−£210,962**	**−£308,388**	**−£387,314**
LAMA: long-acting muscarinic antagonist					

Under a scenario assuming, on average, three prescriptions of tiotropium bromide monohydrate combination packs per patient per year (30 capsules plus HandiHaler® device) the company estimates a total saving of £59,273 in year one, increasing to £405,054 in year five due to the introduction of aclidinium bromide in Wales[1].

5.1.3 AWTTC critique of the budget impact analysis

- The number of patients with COPD in Wales was estimated using prevalence and incidence rates and does not account for mortality in this population group.
- The budget impact analysis presented by the company is based on the assumption that all patients diagnosed with COPD will receive long-acting bronchodilators for maintenance treatment and that 50% of patients are currently managed with tiotropium bromide monohydrate. The basis of this assumption is unclear.
- Therapeutic equivalence is assumed as per the CMA; therefore, only acquisition costs are considered in the analysis.
- Projected uptake is always a source of uncertainty, and so the estimated cost savings are subject to uncertainty.

5.2 Comparative unit costs

Table 4 below provides example comparative costs for the LAMAs used for symptomatic treatment of COPD patients.

Table 4. Examples of acquisition costs of LAMAs used for symptomatic treatment of COPD patients

Treatment	Recommended dose	Approximate cost per year
Aclidinium bromide (Eklira® Genuair®▼) Inhalation powder, 322 micrograms/metered inhalation	1 inhalation twice-daily	**£347.97**
Tiotropium bromide monohydrate (Spiriva®) Inhalation powder, hard capsule (for use with HandiHaler® device), 18 micrograms	18 micrograms (one capsule) once-daily	**£408.95** (including the cost of one HandiHaler®)
Tiotropium bromide monohydrate (Spiriva Respimat®▼) Solution for inhalation, 2.5 micrograms/metered inhalation	5 micrograms (two puffs) once-daily	**£441.29**
Glycopyrronium bromide (Seebri® Breezhaler®▼) Inhalation powder, hard capsule (for use with Breezhaler® device), 60 micrograms	44 micrograms (one capsule) once-daily	**£334.58** (including the cost of Breezhaler®)
Costs of comparators are based on MIMS list prices as of 06 Dec 2012[16]. This table does not imply therapeutic equivalence of the stated drugs and doses. See all relevant SPCs for full dosing details[2,12,13,17].		

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, aclidinium bromide (Eklira® Genuair®▼) may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission highlighted one ongoing study:

- A multiple dose, randomised, double-blind, placebo controlled, two period crossover clinical trial to assess the effect of aclidinium bromide 400 micrograms twice-daily on exercise endurance in patients with stable moderate to severe COPD[18]. The company state that results are expected in Q1 2013[1].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 15 and 19 November 2012.
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Chronic obstructive pulmonary disease (COPD)
COPD is characterised by airflow obstruction. The airflow obstruction is usually progressive, not fully reversible and does not change markedly over several months. The disease is predominantly caused by smoking.

- Airflow obstruction is defined as a reduced post-bronchodilator FEV_1/FVC ratio, such that FEV_1/FVC is less than 0.7.
- If FEV_1 is ≥ 80% predicted, a diagnosis of COPD should only be made in the presence of respiratory symptoms, for example breathlessness or cough[5].

FEV_1
The forced expired volume in 1 second is the volume of air that can be expelled from maximum inspiration in the first second[19].

FEV_1% predicted
The forced expiratory volume in one second (FEV_1) as a percentage of a predicted value, calculated using a reference population[20].

FVC
Forced vital capacity is the volume of air that can be forcibly expelled from the lung from the maximum inspiration to the maximum expiration[19].

St. George's Respiratory Questionnaire (SGRQ)
SGRQ is designed to measure health impairment in patients with asthma and COPD by assessing the frequency of respiratory symptoms and the patient's current state[21].

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