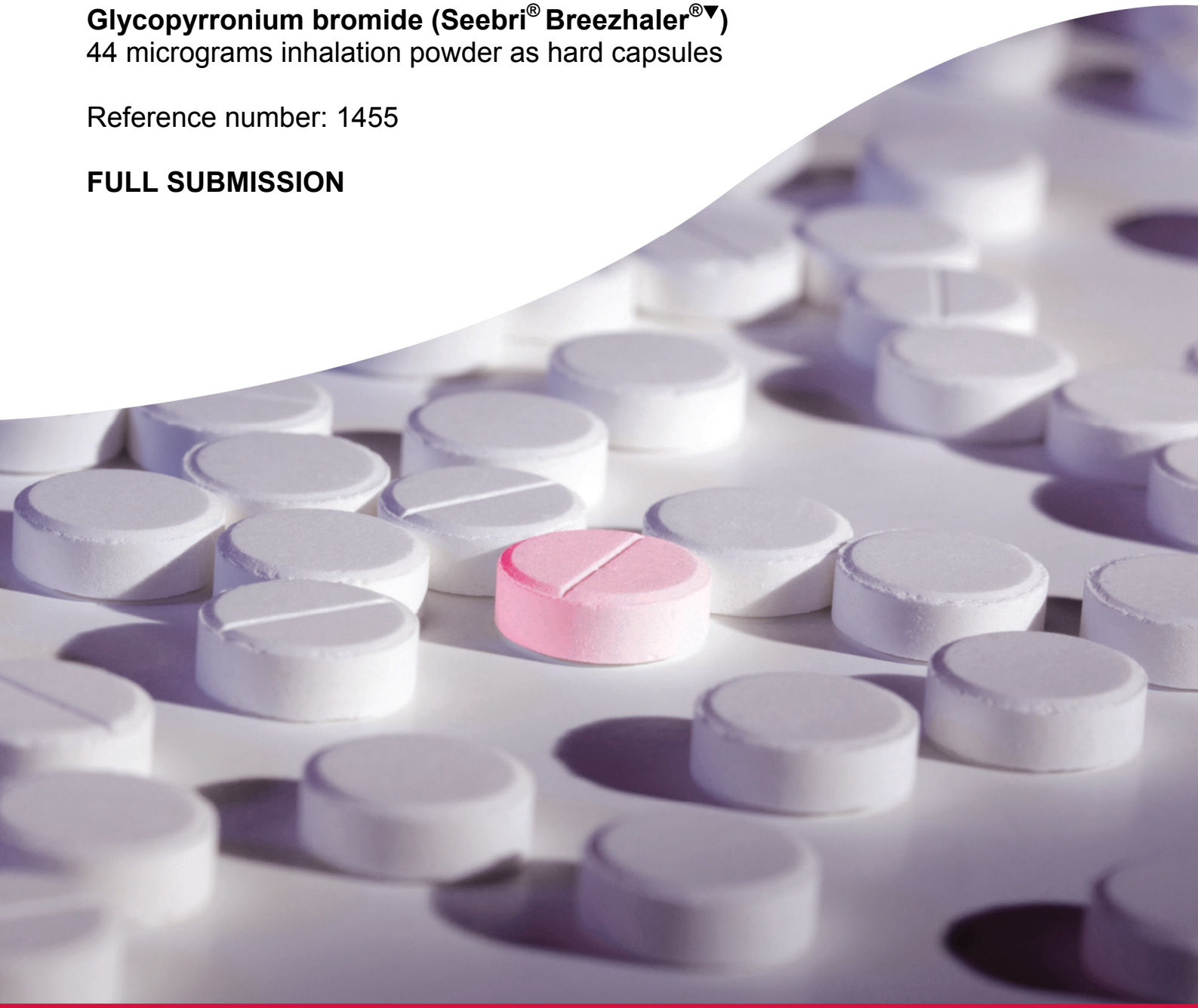
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Glycopyrronium bromide (Seebri® Breezhaler®▼)
44 micrograms inhalation powder as hard capsules

Reference number: 1455

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Glycopyrronium bromide (Seebri® Breezhaler®▼)
44 micrograms inhalation powder as hard capsules

This assessment report is based on evidence submitted by Novartis Pharmaceuticals UK Ltd on 30 October 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Glycopyrronium bromide (Seebri® Breezhaler®▼) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease[2].
Dosing	The recommended dose is the inhalation of the content of one capsule once daily using the Seebri® Breezhaler®▼ inhaler. Each delivered dose contains 55 micrograms of glycopyrronium bromide, which is equivalent to 44 micrograms of glycopyrronium[2].
Marketing authorisation date	28 September 2012[2].

2.0 DECISION CONTEXT

2.1 Background

Chronic obstructive pulmonary disease (COPD) is a chronic disorder characterised by consistent airflow obstruction, which is usually progressive and not fully reversible, and this is associated with persistent and progressive breathlessness, a chronic productive cough and limited exercise capacity. COPD can include a number of conditions, such as chronic bronchitis, emphysema, chronic obstructive airways disease and chronic airflow limitation[3]. The development of COPD is predominately linked to tobacco smoke exposure, but exposure to some chemicals and both organic and inorganic dusts are also known risk factors[4,5]. It is estimated that three million people have COPD in the UK, of which approximately 900,000 have been diagnosed[5]. COPD prevalence increases with age and is rarely seen in people under the age of 35 years[3].

COPD treatment aims to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status and increase exercise tolerance[6]. Bronchodilators are central to the management of COPD symptoms and typically, for moderate to severe COPD, long-acting beta$_2$-agonists (LABA) and long-acting muscarinic receptor antagonists (LAMA) are used[1,4,6]. The addition of a glucocorticosteroid is also recommended as additional therapy for severe COPD[1,4–6]. Glycopyrronium bromide (Seebri® Breezhaler®▼) is a LAMA licensed to relieve symptoms in adult patients with COPD[1].

2.2 Comparators

The comparator requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) was tiotropium (Spiriva®).

2.3 Guidance and related advice

- National Institute for Health and Clinical Excellence (NICE). Evidence summaries: new medicines (ESNM) 9. Chronic obstructive pulmonary disease: glycopyrronium bromide (2013)[7].

- Regional Drug & Therapeutics Centre. Glycopyrronium bromide for chronic obstructive pulmonary disease. New drug evaluation (2012)[8].
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the diagnosis, management and prevention of COPD (2011)[6].
- NICE. Chronic obstructive pulmonary disease. Clinical Guideline 101 (2010)[5].

In May 2013, the All Wales Medicines Strategy Group (AWMSG) will also be considering aclidinium bromide (Eklira® Genuair®▼) as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD[9].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included details from three pivotal phase III clinical trials and an indirect comparison, which described the efficacy and safety of glycopyrronium bromide for the treatment of COPD[1]. The placebo-controlled clinical trials, GLOW-1 and GLOW-3, will not be discussed further as they do not inform the comparison of glycopyrronium bromide with tiotropium.

3.1 GLOW-2

GLOW-2 was a multicentre, randomised, double-blind, placebo-controlled with open label tiotropium arm, parallel-group phase III trial designed to assess the efficacy and safety of glycopyrronium bromide in patients (≥ 40 years) with moderate to severe COPD over 52 weeks. Patients (n = 1,066) were randomised 2:1:1 to receive one of three once daily treatments: glycopyrronium bromide (50 micrograms delivered via single-dose dry powder inhaler [SDDPI]), placebo (delivered via SDDPI) or open-label tiotropium (18 micrograms administered via the Handihaler®). Efficacy was assessed in the full analysis set, which included all randomised patients who received at least one dose of the study treatment (glycopyrronium bromide n = 525; placebo n = 268; tiotropium n = 267)[4,10].

The primary endpoint was trough forced expired volume in one second (FEV_1; see Glossary) defined as mean evaluation at 23 hours 15 minutes and 23 hours 45 minutes after dosing at week 12. This was statistically higher in the glycopyrronium bromide arm (1.469 litres) compared with the placebo arm (1.372 litres) with a treatment difference of 0.097 litres ($p < 0.001$). A similar improvement in FEV_1 was seen in the tiotropium arm (1.455 litres versus 1.372 litres in the placebo group; treatment difference 0.083 litres; $p < 0.001$)[4,10–12]. This was supported by statistically significant improvements versus placebo 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) at 26 weeks[4,10] (see Table 1). The treatment difference considered to be clinically important for breathlessness (≥ 1 point improvement in TDI score) and health related quality of life (SGRQ total score reduction ≥ 4 points) was not reached for glycopyrronium bromide versus placebo or for tiotropium versus placebo[4,10].

As an additional analysis, a comparison between glycopyrronium bromide and tiotropium was carried out; this was not powered to show statistical superiority. At 12 weeks, a treatment difference of 0.014 litres ($p = 0.399$) was observed between the groups[10].

Table 1. Results of the GLOW-2 phase III trial (full analysis set)[4,10–12].

	Treatment arms			Treatment difference (Least squares mean)		
	Glycopyrronium bromide	Placebo	Tiotropium	Glycopyrronium vs placebo	Tiotropium vs placebo	Glycopyrronium vs tiotropium
Primary endpoint						
Trough FEV_1 at 12 weeks (litres)	1.469	1.372	1.455	0.097 p < 0.001	0.083 p < 0.001	0.014 p =0.399
Secondary endpoints						
Dyspnoea at 26 weeks (total score)	2.13	1.32	2.26	0.81 p = 0.002	0.94 p = 0.002	−0.13
SGRQ outcome at 52 weeks (total score)	40.85	44.16	41.32	−3.32 p < 0.001	−2.84 p = 0.014	−0.48
Time to first moderate or severe COPD exacerbation	-	-	-	Hazard ratio 0.66 p = 0.001	Hazard ratio 0.61 p = 0.001	-
Number of patients ≥ 1 COPD exacerbation during 52 weeks	172/524 (32.8%)	107/266 (40.2%)	80/266 (30.1%)	-	-	-
Change from baseline in mean daily rescue medication use over 52 weeks (puffs per day)	−1.58	−1.20	−1.83	−0.37 p = 0.039	−0.63 p = 0.003	0.25

3.2 Indirect comparison

As there were no data directly comparing glycopyrronium bromide to tiotropium, an indirect treatment comparison (a Bayesian network meta-analysis) has been included in the company submission to evaluate the relative efficacy of the two treatments in patients with moderate to severe COPD[1]. The comparison utilised data from 21 studies involving either glycopyrronium bromide or tiotropium (including GLOW-1 and GLOW-2), which were derived from a systematic review. Results of the Bayesian network meta-analysis are commercial in confidence.

3.3 Comparative safety

The safety of glycopyrronium bromide has been evaluated in the three phase III trials, GLOW-1, GLOW-2 and GLOW-3[10,13,14]. The incidence of adverse events (AEs) was generally comparable across all treatment groups for each study. Comparative safety information was obtained from the GLOW-2 trial[10]. In this study, the most frequently reported AEs were worsening COPD (36.4% in the glycopyrronium bromide arm versus 33.7% in tiotropium arms; incidence in the placebo arm was 43.3%), nasopharyngitis (9.0% versus 7.9% respectively; 5.6% in the placebo arm) and upper respiratory tract infection (10.9% versus 11.2%; 12.3% in the placebo arm)[10].

AEs such as cough, dry mouth, gastrointestinal and or urinary tract disturbances were also commonly seen during clinical trials[2]. In the GLOW-1 trial, notable changes in electrocardiograph (ECG) QTcF intervals were reported in 4.0% of patients treated with glycopyrronium bromide compared to 1.1% of those treated with placebo[13]. However, in GLOW-2, the percentage of patients with newly occurring, or worsening clinically notable QTcF intervals were comparable between treatment groups (4.4% glycopyrronium bromide, 5.3% tiotropium and 6% placebo)[10]. Atrial fibrillation, when reported as an AE, occurred more frequently in the glycopyrronium bromide arm than the placebo arm[4]. However, it was noted that all four cases of atrial fibrillation found in the glycopyrronium bromide arm were considered not to be related to the study drug; three out of four of the patients had pre-existing cardiovascular disorders prior to entering the study. Analysis of the ECG recordings revealed that atrial fibrillation was similar in both treatment groups. Information was added to the Summary of Product Characteristics (SPC) and included in the Risk Management Plan as a potential risk[4].

The Committee for Medicinal Products for Human Use (CHMP) noted that the frequency and nature of AEs was generally considered to be typical for a moderate to severe COPD population. However, in view of the potential risk of cardiovascular outcomes, CHMP requested a post-authorisation safety study to monitor cardiovascular and cerebrovascular outcomes post-marketing[4].

3.4 AWTTC critique

- Owing to the lack of a direct comparison between glycopyrronium bromide and tiotropium, the company submission includes an indirect comparison[1]. While this is a common approach to overcome the lack of direct comparative data, indirect comparisons have inherent limitations.
- As an additional analysis in the GLOW-2 trial, a comparison was made between glycopyrronium bromide and tiotropium. It should be noted that this analysis was not powered to show statistical superiority. However, the analysis demonstrated that outcomes were comparable between patients treated with glycopyrronium bromide and those in the tiotropium group[10].
- There was no long-term follow-up of patients treated with glycopyrronium bromide in the clinical studies and so information on efficacy and safety is limited to 52 weeks[4,10].
- In their submission, the applicant company have provided data supporting the use of glycopyrronium bromide in moderate to severe COPD[1]. However, the licensed indication does not specify disease severity[2]. It is not clear whether

the outcomes seen in the clinical trials would adequately reflect the whole licensed population.

- In their submission, the applicant company highlighted that it was difficult to design a double-blind study involving tiotropium. In the clinical studies, recruited patients placed the treatment capsule into the inhalation device and were subsequently able to identify the logo of the tiotropium marketing authorisation holder (Boehringer Ingelheim Ltd). The applicant company state that it was not possible to produce active tiotropium without the logo owing to product stability concerns; production of a placebo with the logo was also not possible due to trademark protection[1].
- GLOW-2 included an open-label tiotropium arm, in addition to the double-blinded glycopyrronium bromide and placebo groups[10]. The company state that the use of open-label tiotropium did not introduce bias on objective outcome measures such as trough FEV_1. However, minimal bias may have been introduced for subjective measures, such as TDI and SGRQ[1].
- Although the efficacy of the once daily glycopyrronium bromide (50 microgram) regimen has been demonstrated, some limited data suggest that a twice daily, 25 microgram regimen could be more efficacious. CHMP has requested a post-authorisation clinical study to further characterise the optimal dosing schedule. This study will be a multicentre, randomised, double-blind, parallel group study designed to compare the efficacy, safety and tolerability of glycopyrronium bromide 44 micrograms given once daily and 25 micrograms administered twice daily in patients with stable COPD and moderate to severe airflow obstruction. The study duration will be 26 weeks[4].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] describes a cost minimisation analysis (CMA) of glycopyrronium bromide, used with the Breezhaler® airflow inhalation device, in its licensed indication as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. The comparators used in the analysis are tiotropium 18 micrograms (Spiriva®) inhalation powder and tiotropium 5 micrograms (Spiriva® Respimat®▼) solution for inhalation.

The company analysis is based on the assumption of therapeutic equivalence between glycopyrronium bromide and the comparators, as evidenced by a network meta-analysis (see Section 3.2)[1]. Assessed clinical outcomes included trough FEV_1, exacerbation rates, dyspnoea, and health related quality of life measured using SGRQ. Equivalency of AE profile is also assumed based on the results of the GLOW-2 trial[11,12] which compared glycopyrronium bromide versus placebo, over 52 weeks, with open-label tiotropium (see Section 3.1).

Only drug acquisition costs, based on MIMS[15] prices, were considered in the analysis. The analysis is conducted over a five-year time horizon. Costs are discounted at 3.5%, with sensitivity analyses using 0% and 6% discount rates also presented.

4.1.2 Results of the company's analyses

The base case CMA results are presented in Table 2. These show that glycopyrronium bromide is cost saving compared to both tiotropium formulations (18 micrograms Spiriva® inhalation powder and 5 micrograms Sipriva® Respimat®) under the assumption of therapeutic equivalence. The results of sensitivity analyses examining the impact of varying the discount rate (0% and 6%) are also presented.

Table 2. Company-reported CMA results.

	Glycopyrronium bromide	Spiriva® inhalation powder	Glycopyrronium vs Spiriva® inhalation powder	Spiriva® Respimat®▼	Glycopyrronium vs Spiriva® Respimat®▼
Total treatment costs per patient (first year)	£334.58	£408.95	**−£74.37**	£431.92	**−£97.34**
Total five-year costs (3.5% discount)	£1,563.49	£1,911.03	**−£347.54**	£2,018.35	**−£454.86**
Total five-year costs (0% discount)	£1,672.90	£2,044.75	**−£371.85**	£2,159.60	**−£486.70**
Total five-year costs (6% discount)	£1,493.80	£ 1,825.84	**−£332.04**	£1,928.39	**−£434.59**

4.1.3 AWTTC critique of the economic evidence

The reliability of the CMA presented by the company is dependent upon the extent to which glycopyrronium bromide is considered to have been demonstrated to be therapeutically equivalent to tiotropium. The company based its assumption of therapeutic equivalence on a systematic review and network meta-analysis. This incorporates the direct comparative data from the GLOW-2 trial and indirect data from other relevant studies, and can be considered the most appropriate source of clinical evidence. There were no statistically significant differences in lung function measures, exacerbation rates and quality of life estimates, but credible intervals around relative exacerbation rates are relatively wide. The CMA framework precludes exploration of the impact of this uncertainty.

Strengths of the economic evidence:

- A network meta-analysis based on a systematic review of randomised controlled trial evidence has been conducted to support the assumption of therapeutic equivalence with tiotropium. Outcomes considered in the analysis included objective lung function measures, exacerbation rates, and subjective measures of symptoms and quality of life.

Limitations of the economic evidence:

- Adjustments for differences in baseline characteristics among the trials included in the network meta-analyses was undertaken, but estimates of relative exacerbation rates, which are key clinical and economic events, are characterised by relatively wide credible intervals, and therefore are subject to uncertainty that may not be further explored in a CMA framework. AE profiles are assumed to comparable based on the limited data from the GLOW-2 trial.
- The maximum follow up period for the randomised controlled trials included in the network meta-analysis is 12 months.
- The results of the network meta-analysis apply only to patients with moderate to severe COPD, as studies in patients with mild COPD were excluded from the analysis.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-effectiveness of glycopyrronium bromide within its current licensed indication.

5.0 ASSESSMENT OF THE EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Using Quality and Outcomes Framework (QOF) data[16] and Wales population projections[17], the applicant company reports that the number of COPD patients registered in Wales in 2011–2012 is 66,951 patients, representing approximately 2% of the Welsh population[1]. To extrapolate the number of patients beyond 2012, the company utilised an estimate of COPD incidence of 84 per 100,000, based on a global burden of disease study[18]. Assuming a constant incidence over the coming five years and using mortality estimates from StatsWales, the company estimates that the total number of COPD patients in Wales will increase from 67,920 at the end of 2012 to 72,979 at the end of 2017. Prescribing data indicate that 44,064 patients (64.88%) currently receive the comparator, tiotropium, in Wales[19]. This percentage estimate is used to extrapolate the number of patients expected to use tiotropium in Wales over the next five years. Based on marketing forecasts, the company estimates that 0.2% of patients will switch to glycopyrronium bromide in year one (2012). This is expected to increase gradually to reach 5.7% in year five (2016).

5.1.2 Results of company's budget impact analysis

The company anticipates cost saving to result from using glycopyrronium bromide in place of current comparators. The results are summarised in Table 3 below.

Table 3. Company-reported costs associated with the use of glycopyrronium bromide.

	Year 1 (2012)	Year 2 (2013)	Year 3 (2014)	Year 4 (2015)	Year 5 (2016)
Number of eligible patients	45,135	45,135	44,701	45,348	46,005
Uptake (%)	0.2%	1.3%	2.8%	4.3%	5.7%
Treated patients*	90	581	1270	1978	2660
Net costs per patient					
Medication costs	−£7,118	−£45,824	−£100,126	−£155,990	−£209,772
Administration, monitoring, all other costs	Assumed equal	Assumed equal	Assumed equal	Assumed equal	Assumed equal
Overall net cost	−£7,118	−£45,824	−£100,126	−£155,990	−£209,772

5.1.3 AWTTC critique of the budget impact analysis

- The company has made reasonable effort to define the epidemiology of COPD in Wales and to identify the target patient population using Welsh QOF[16] and prescribing data[19].
- The analysis provided takes into account patients switching from Spiriva® inhalation powder and Spiriva® Respimat®▼ to glycopyrronium bromide. Projected uptake is always a source of uncertainty.
- Patients continuing to be maintained on glycopyrronium bromide are not considered in the analysis. Hence, the patient numbers may be underestimated but this would only underestimate the cost savings expected.

5.2 Table of 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.

Drug	Recommended dose	Approximate cost per year
Glycopyrronium (as bromide) (Seebri® Breezhaler®▼) Inhalation powder, hard capsule (for use with Breezhaler® device), 60 micrograms glycopyrronium bromide (equivalent to 50 micrograms)	44 micrograms (one capsule) daily	**£334.58** (including the cost of Breezhaler®)
Tiotropium (as tiotropium bromide monohydrate) (Spiriva®) Inhalation powder, hard capsule (for use with HandiHaler® device), 18 micrograms	18 micrograms (one capsule) daily	**£408.95** (including the cost of one HandiHaler®)
Tiotropium (as tiotropium bromide monohydrate) (Spiriva® Respimat®▼) solution for inhalation, 2.5 micrograms/metered inhalation	5 micrograms (two puffs) once daily	**£441.29**
Aclidinium bromide (Eklira® Genuair®▼) Inhalation powder, 400 micrograms/metered inhalation	1 inhalation twice daily	**£347.97**
Costs of comparators are based on MIMS list prices as of 06 Dec 2012[15]. This table does not imply therapeutic equivalence of the stated drugs and doses. See all relevant SPCs[2,20–22] for full dosing details.		

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

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

6.2 Ongoing studies

The company submission highlighted ongoing studies that are likely to be available within 6–12 months[1]:

- GLOW-5: Glycopyrronium bromide versus blinded tiotropium[23].
- GLOW-6: Glycopyrronium bromide as add-on to LABA/inhaled corticosteroids combination[24].
- SPARK study: Reducing exacerbations in COPD. This study uses glycopyrronium bromide specific data (also includes indacaterol/glycopyrronium fixed combination product)[25].
- SHINE study: A multicentre 26-week study using indacaterol/glycopyrronium fixed combination product, indacaterol, glycopyrronium and open-label tiotropium versus placebo[26].

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 November 2012

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

GLOSSARY

Chronic obstructive pulmonary disease (COPD)
National Institute for Health and Clinical Excellence (NICE) use the following working definition of COPD:

- Airflow obstruction is defined as a reduced 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[27].

FEV_1% predicted
The forced expiratory volume in one second (FEV_1) expressed as a percentage of a predicted value, calculated using a reference population[27].

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[27].

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