Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

glycopyrronium 44 micrograms hard capsules of inhalation powder (Seebri Breezhaler®) SMC No. (829/12)

Novartis Pharmaceuticals Ltd.

07 December 2012

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

ADVICE: following a full submission

glycopyrronium inhalation powder (Seebri Breezhaler®) is accepted for use within NHS Scotland.

Indication under review: as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

In two phase III studies, glycopyrronium was statistically superior to placebo in improving lung function (forced expiratory volume in 1 second [FEV_1]) after 12 weeks.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

As a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Dosing Information

The contents of one capsule (44 micrograms) inhaled once daily using the Seebri Breezhaler® inhaler.

Product availability date

02 November 2012

Summary of evidence on comparative efficacy

Chronic obstructive pulmonary disease (COPD) is characterised by airflow obstruction that is usually progressive, not fully reversible, and does not change markedly over several months. Glycopyrronium is a long-acting muscarinic antagonist which blocks the bronchoconstrictor action of acetylcholine on airways smooth muscle to induce bronchodilation. This is a new formulation of glycopyrronium which has been available as an oral powder for hyperhidrosis and as an injection for use in anaesthesia.

The evidence to support the efficacy of inhaled glycopyrronium in COPD comes from the results of two similarly designed phase III studies: one of 26 week duration (GLOW 1)[1] and one of 52 week duration (GLOW 2).[2] Both studies enrolled patients aged ≥40 years who were current or former cigarette smokers (smoking history of ≥10 pack-years) and had a diagnosis of COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. Eligible patients had post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of <0.7, and FEV_1 ≥30% and <80% of predicted (i.e. moderate to severe COPD). In GLOW 1, patients were randomised to receive glycopyrronium 50 micrograms once daily or placebo (delivered by the Breezhaler® device) in a ratio of 2:1 for 26 weeks. While in GLOW 2, patients were randomised to receive glycopyrronium 50 micrograms once daily or placebo (delivered by the Breezhaler® device) or open-label tiotropium 18 micrograms once daily as an active control, (delivered by the Handihaler® device) in a ratio of 2:1:1 for 52 weeks. However, this study was not designed to compare glycopyrronium with tiotropium. The 50 micrograms metered dose of glycopyrronium (as bromide) used in the clinical studies is equivalent to the delivered dose of 44 micrograms glycopyrronium stated in the summary of product characteristics. The intention to treat population comprised 822 patients in GLOW 1 and 1,066 in GLOW 2. During the studies, patients were allowed to use salbutamol/albuterol as needed and to continue to use the following concomitant medicines provided they had been at stable doses before screening: inhaled or intranasal corticosteroids and $histamine_1$ antagonists. Other long-acting bronchodilator therapy was not permitted during the study.

The primary outcome was trough FEV_1 at week 12 in both studies. In GLOW 1, the change from baseline in trough FEV_1 at week 12 was significantly greater with glycopyrronium compared with placebo, with a least squares mean (LSM) ± standard error (SE) improvement of

108 ± 14.8mL (p<0.001). The treatment difference was also significant at the end of day 1 and at week 26 (105mL and 113mL, respectively, p<0.001 for both comparisons).[1] In GLOW 2, the change from baseline in trough FEV_1 at week 12 was significantly greater with glycopyrronium and tiotropium compared with placebo with a mean improvement of 97mL (95% confidence interval [CI]: 0.065 to 0.130) and 83mL (95% CI: 0.046 to 0.121) respectively (p<0.001 for both comparisons).[2]

Key secondary endpoints included the Transition Dyspnoea Index (TDI) score and the St George's Respiratory Questionnaire (SGRQ). The TDI assesses symptom relief and is a sum of three domains (functional impairment, magnitude of task and magnitude of effort) with a score range of -9 to 9, where negative scores indicate deterioration. In both studies, there was a statistically significant improvement from baseline in mean TDI focal score in the glycopyrronium group compared with placebo at 26 weeks: treatment difference 1.04 units in GLOW 1 and 0.81 units in GLOW 2 (0.94 units for tiotropium versus placebo). An improvement of ≥1 unit in TDI focal score is considered clinically significant and this was reported in significantly more glycopyrronium than placebo patients: 61% versus 48%, respectively, in GLOW 1 and 55% versus 44% respectively (53% with tiotropium) in GLOW 2.[1,2] The SGRQ is a self-administered 50-item survey encompassing three components (symptoms, activity and social or psychological impacts with scores ranging from 0 [best] to 100 [worst]). The results demonstrated that glycopyrronium was statistically superior to placebo in both studies with a mean improvement over placebo of 2.8 in GLOW 1 at week 26 and 3.3 in GLOW 2 at week 52 (2.8 with tiotropium versus placebo). The proportion of patients achieving a clinically significant difference (defined as an improvement of at least 4 units) was significant at week 26 in GLOW 1 (57% versus 46%) but not at week 52 in GLOW 2 (55% versus 51% and 59% for tiotropium).[1,2]

There was a reduction in moderate to severe COPD exacerbations (requiring antibiotics or corticosteroids or hospitalisation) with glycopyrronium versus placebo in both studies. In GLOW 1, there was a numerical reduction in the annualised rate of moderate or severe COPD exacerbations at 26 weeks: 0.43 versus 0.59 per year respectively (rate ratio: 0.72, p=0.071). In GLOW 2, the annualised rate of moderate or severe COPD exacerbations was significantly reduced in the glycopyrronium group at 52 weeks: 0.54 versus 0.80 per year respectively (rate ratio: 0.66, p=0.003) but not in the tiotropium group (rate ratio: 0.80, p=0.179). A pooled analysis of data to 26 weeks from GLOW 1 and 2 found that glycopyrronium decreased the annual rate of moderate and severe exacerbations to 0.53 compared with 0.77 with placebo (p<0.001). This analysis also found that the incidence of patients with COPD exacerbations requiring hospitalisation was significantly lower with glycopyrronium than placebo (1.7% versus 4.4%, p=0.003). In both studies, the use of rescue medication with salbutamol/albuterol was significantly reduced in the glycopyrronium group by 0.37 to 0.46 puffs/day compared with placebo.

A third, randomised, phase III, study (GLOW 3) compared the effects of glycopyrronium with placebo on exercise tolerance in 108 patients with moderate to severe COPD. Eligible patients were randomised, in a cross-over design, to receive glycopyrronium 50 micrograms daily followed by placebo or placebo followed by glycopyrronium 50 micrograms daily for 3 weeks with a 14 day washout. The primary endpoint of exercise tolerance measured by submaximal constant-load cycle ergometry testing on day 21, was significantly improved by glycopyrronium with a LSM difference of 88.9 seconds (21%).[3]

Summary of evidence on comparative safety

The two key studies primarily compared glycopyrronium with placebo but the GLOW 2 study also included open-label tiotropium.

In GLOW 1, the main difference between the incidences of adverse events appeared to be related to the higher incidence of COPD worsening in the placebo (27%) compared with the glycopyrronium group (20%). The incidence of potential antimuscarinic adverse effects (gastrointestinal disturbances, urinary difficulty, urinary retention and dry mouth) was reported to be similar in both groups although actual incidences were not stated.[1]

In GLOW 2, COPD worsening was the most frequently reported adverse event and had a higher incidence in the placebo group (43%) than in the glycopyrronium (36%) and tiotropium (34%) groups. The incidence of antimuscarinic adverse effects (constipation, urinary tract infection, urinary retention and dry mouth) was reported to be low in all three groups. The incidences were only reported for dry mouth (3.0% in glycopyrronium, 1.9% in placebo and 1.5% in tiotropium patients) and urinary tract infection (2.7%, 3.0% and 6.0% respectively).[2] The risk of exacerbations in terms of time to first moderate or severe exacerbation was significantly reduced with glycopyrronium versus placebo (HR: 0.66, p=0.001) and with tiotropium versus placebo (HR: 0.61, p=0.001).

In a core 6-month safety database including 1,075 glycopyrronium, 535 placebo and 267 tiotropium patients, the European Public Assessment Report noted that the incidence of dry mouth was numerically higher with glycopyrronium.[4]

Summary of clinical effectiveness issues

Glycopyrronium is a new inhaled long-acting muscarinic antagonist (LAMA) for the treatment of COPD. Two clinical studies primarily compared lung function (assessed by FEV_1) for glycopyrronium and placebo and results demonstrated significant improvements. The European Medicines Agency (EMA) recommends that there should be co-primary endpoints assessing lung function and symptom-based outcomes. Patient-orientated outcomes (SGRQ, TDI, COPD exacerbations) were assessed as key secondary endpoints. GLOW 2 was sufficiently powered to detect differences in the key secondary endpoints.

The EMA notes that there is no general agreement on the degree of change in lung function that is considered to be clinically relevant. Glycopyrronium resulted in mean changes from baseline relative to placebo of 97 to 108mL, which are marginally lower than the 120ml level considered to be clinically relevant by some sources. Results were only available for change from baseline values and baseline values, to indicate the relative effect, were not reported.

However, the aim of COPD treatment is to reduce exacerbation rates and slow the decline in health status and not to improve lung function per se. Therefore, the secondary, patient-focused, endpoints are clinically relevant. The reduction in moderate to severe COPD exacerbations was significantly different between glycopyrronium and placebo in only one study but, in a pooled analysis, the difference achieved statistical significance. At baseline, 73% to 78% of study patients had experienced no moderate or severe exacerbations in the year before

screening. Therefore the effect on reducing exacerbation rate is likely to be modest in these patients.

Study patients had moderate to severe COPD so there is a lack of phase III data in patients with very severe disease. Although the durations of the studies were 26 and 52 weeks, the primary endpoint was measured at 12 weeks, which is relatively short for a chronic disease. However, data to one year suggest that the bronchodilator effect is maintained. Since patients with a history of certain cardiovascular diseases were excluded from both studies, the summary of product characteristics states that glycopyrronium should be used with caution in these patient groups.

The GLOW 2 study included an open-label tiotropium control arm and although the study was not designed to compare the two active agents, their efficacy appeared similar. However the unblinded use of tiotropium may have introduced bias.

There are no direct blinded clinical data comparing glycopyrronium with an active comparator, either tiotropium or the recently licensed aclidinium. An indirect comparison of glycopyrronium versus tiotropium was presented using a Bayesian network meta-analysis (NMA) model. Indirect evidence only was included and the common reference comparator was placebo. Two glycopyrronium studies, 16 tiotropium 18 microgram and three tiotropium 5 microgram studies were included and a number of primary and secondary outcomes analysed; FEV_1 and FVC values, TDI, SGRQ and COPD exacerbations. The analysis presented efficacy outcomes only, with no examination of adverse event profiles. Although broadly similar there was significant between study heterogeneity but no sensitivity analysis was presented. The conclusion from the analyses was that 12 and 24 weeks treatment with glycopyrronium was non-inferior to tiotropium in terms of its efficacy as a once-daily maintenance bronchodilator treatment to relieve symptoms in patients with COPD.

Glycopyrronium would offer an alternative inhaled LAMA to tiotropium and aclidinium for COPD patients. Tiotropium is inhaled once daily and aclidinium requires twice daily dosing. Glycopyrronium is delivered by the Breezhaler® device, a single-dose inhaler which should be disposed of after 30 days of use. This device is currently available for the long-acting beta-agonist, indacaterol (Onbrez®). However patients new to this device will require training to ensure satisfactory technique. Since the clinical studies excluded patients with certain cardiovascular conditions, glycopyrronium should be used with caution in such patients (see summary of product characteristics for details).

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing glycopyrronium with tiotropium (18 micrograms and 5 micrograms) as maintenance treatment of COPD. A one year time horizon was used for the analysis.

The clinical evidence to support the use of a cost-minimisation analysis came from the results of a Bayesian network meta-analysis that showed glycopyrronium is expected to be comparable to tiotropium (18 micrograms and 5 micrograms) with respect to all clinical parameters evaluated.

The analysis compared the total cost per patient per year for glycopyrronium versus tiotropium. Only drug acquisition costs were included in the analysis.

The results showed that the total cost per patient per year is £334.58 for glycopyrronium compared to £408.95 for tiotropium 18 micrograms and £431.92 for tiotropium 5 micrograms. On this basis glycopyrronium would therefore be the preferred treatment on cost-minimisation grounds. Sensitivity analysis was not provided given the simple nature of the analysis, but there were no major concerns noted. As such, the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) published clinical guideline 101 on the management of COPD in adults in primary and secondary care in June 2010.[5] This guideline recommends:

- initial treatment with a short-acting bronchodilator when required.
- once-daily LAMA should be offered in preference to four-times-daily short-acting muscarinic antagonist (SAMA) to people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required, and in whom a decision has been made to commence regular maintenance bronchodilator therapy with a muscarinic antagonist.
- in patients with stable COPD and $FEV_1 \geq 50\%$ predicted who remain breathless or have exacerbations either a long-acting beta-agonist (LABA) or LAMA is recommended.
- if these patients still remain breathless or have exacerbations consider LABA+ inhaled corticosteroid (ICS) in a combination inhaler or LAMA in addition to LABA where ICS is declined or not tolerated.
- in patients with stable COPD $FEV_1 < 50\%$ predicted who remain breathless or have exacerbations on short-acting bronchodilators either LABA+ICS in a combination inhaler, or LAMA is recommended.
- if patients still remain breathless or have exacerbations despite taking LABA+ICS, irrespective of their FEV_1 a LAMA in addition to LABA+ICS should be considered.
- the choice of drug(s) should take into account the patient's response to a trial of the drug, the drug's side effects, patient preference and cost.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) published revised guidelines "Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease" in 2011. [6] This guideline recommends the following first and second choice options according to the patient's COPD:

- for patients with low risk of exacerbations and fewer symptoms: first choice - shorting-acting bronchodilators as required or SAMA; second choice - LAMA or LABA or SAMA + SABA
- for patients with low risk of exacerbations and more symptoms: first choice - LAMA or LABA; second choice -LAMA + LABA
- for patients with high risk of exacerbations and fewer symptoms: first choice - LAMA or ICS + LABA; second choice - LAMA + LABA

- for patients with high risk of exacerbations and more symptoms: first choice - LAMA or ICS + LABA; second choice - ICS + LAMA or ICS + LABA +LAMA or ICS +LABA + phosphodiesterase inhibitor or LAMA + LABA or LAMA + phosphodiesterase inhibitor

Additional information: comparators

The main comparator is tiotropium, which was the only other LAMA available until aclidinium became available in September 2012. Other long-acting bronchodilators include the LABAs, salmeterol and formoterol.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Glycopyrronium (Seebri Breezhaler®)	**44 micrograms inhaled once daily**	**330**
Tiotropium (Spiriva Respimat®)	5 micrograms inhaled once daily	426
Tiotropium (Spiriva Handihaler)	18 micrograms inhaled once daily	403*
Aclidinium (Eklira Genuair®)	322 micrograms inhaled twice daily	343

Doses are for general comparison and do not imply therapeutic equivalence. Costs are taken from eMIMS October 2012 except for glycopyrronium which is from the company submission. * cost for tiotropium (Spiriva Handihaler®) includes one device.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 77,450 in year 1 rising to 82,424 in year five with an estimated uptake rate of 1.3% in year 1 and 6.7% in year 5. The gross impact on the medicines budget was estimated to be £337k in year 1 and £1.848m in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to result in savings of £78k in year 1 and £428k in year 5.

References

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

1. D'Urzo A, Ferguson GT, van Noord JA et al. Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: the GLOW1 trial. Respiratory Research 2011;12:156.

2. Kerwin E, Hebert J, Gallagher N et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with moderate-to-severe COPD over 52 weeks: The GLOW 2 study. European Respiratory Journal 2012 as doi: 10.1183/09031936.00040712

3. Beeh KM, Singh D, Scala LD et al. Once-daily NVA237 improves exercise tolerance from the first dose in patients with COPD: the GLOW 3 trial. International Journal of COPD 2012;7:503-513.

4. European Medicines Agency. European Public Assessment Report for Seebri Breezhaler® EMEA/H/C/002430. www.ema.europa.eu [accessed 29 October 2012]

5. NICE COPD Guidelines 2010 (CG101). National Institute for Health and Clinical Excellence (NICE)

6. GOLD Guidelines (2011). Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 www.goldcopd.org

This assessment is based on data submitted by the applicant company up to and including 14 November 2012.

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

Advice context:

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

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