NICE advice

Chronic obstructive pulmonary disease: glycopyrronium bromide

Evidence summary
Published: 7 January 2013
nice.org.uk/guidance/esnm9

Overview

The content of this evidence summary was up-to-date in January 2013. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Key points from the evidence

Glycopyrronium bromide (Seebri Breezhaler) is an inhaled long-acting muscarinic antagonist (LAMA) for maintenance bronchodilator treatment to relieve symptoms in adults with chronic obstructive pulmonary disease (COPD). It received a European marketing authorisation in September 2012 and was launched in the UK in November 2012.

In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, the NICE guideline on Chronic obstructive pulmonary disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update) (NICE clinical guideline 101) advises that maintenance therapy can be provided by the following (alone or in combination, with choice depending on several factors; see guideline for details):

- a long-acting beta$_2$ agonist (LABA)
- a LAMA

- a LABA with an inhaled corticosteroid (ICS) in a combination inhaler.

Evidence from 2 phase III placebo-controlled studies (GLOW1 [n=822, 26 weeks] and GLOW2 [n=1066, 52 weeks]) in patients with moderate to severe COPD, showed a statistically significant improvement in the disease-oriented primary end point, 12-week trough FEV_1 (forced expired volume in 1 second), with glycopyrronium bromide compared with placebo (least squares mean difference 108 ml and 97 ml respectively, both $p<0.001$). These differences are around the level considered to be clinically relevant (minimum clinically important difference 100 ml).

In both studies, a statistically significant difference was seen for the key secondary patient-oriented outcomes, breathlessness and health status. However, the effect sizes for these measures were small. The difference considered to be clinically important for health status was not reached in GLOW1 or GLOW2. For breathlessness, the difference considered to be clinically important was achieved in GLOW1 but not in GLOW2.

GLOW2 included an open-label comparison with another LAMA, tiotropium. Tiotropium was statistically significantly more effective than placebo for the primary and 2 key secondary outcomes, showing similar results to glycopyrronium bromide. No significant differences were seen between glycopyrronium bromide and tiotropium for these outcomes.

A number of anticholinergic adverse events were seen with glycopyrronium bromide, particularly dry mouth, but generally the excess numbers compared with placebo were low.

More robust evidence comparing patient-orientated outcomes for glycopyrronium bromide with other active treatments for COPD would enable its place in therapy to be more clearly established. Local decision makers will need to consider the evidence for glycopyrronium bromide alongside that for the other treatments for COPD. Individual patient factors and the costs and safety profile of each treatment will need to be taken into account.

Key evidence

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

Kerwin E, Hébert J, Gallagher N et al. (2012) Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. European Respiratory Journal 40: 1106–14

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

Relevance to NICE guidance programmes

Glycopyrronium bromide was not considered appropriate for a NICE technology appraisal and is not currently planned into any other work programme.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by airflow obstruction that is usually progressive and not fully reversible; it is predominantly caused by smoking[1]. COPD is a common cause of death and long-term disability. According to GP registers, there were nearly 900,000 patients with COPD in England in 2010/11[2]. During the same period there were approximately 120,000 hospital admissions in England in which COPD was the primary diagnosis[3].

The NICE clinical guideline on COPD defines COPD as follows:

- Airflow obstruction is defined as a reduced FEV_1/FVC ratio (where FEV_1 is forced expired volume in 1 second and FVC is forced vital capacity), such that FEV_1/FVC is less than 0.7.
- If FEV_1 is at least 80% predicted normal, a diagnosis of COPD should only be made in the presence of respiratory symptoms, for example breathlessness or cough.

Classification of severity of airflow obstruction in COPD according to NICE guidance is shown in table 1.

Table 1 Classification of severity of airflow obstruction in COPD

Severity of airflow obstruction		
Post-bronchodilator FEV_1/FVC	FEV_1 % predicted	Post-bronchodilator
<0.7	≥80%	Stage 1: Mild[a]

<0.7	50–79%	Stage 2: Moderate
<0.7	30–49%	Stage 3: Severe
<0.7	<30%	Stage 4: Very severe[b]

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expired volume in 1 second; FVC, forced vital capacity.

[a] Symptoms should be present to diagnose COPD in people with mild airflow obstruction.

[b] Or FEV_1 <50% with respiratory failure.

The NICE clinical guideline on COPD advises that all patients who are still smoking should be encouraged to stop, and offered help to do so, at every opportunity. The guideline recommends the following inhaled treatments for managing people with stable COPD. The list is not comprehensive but does include the key recommendations that relate to this evidence summary and the likely place in therapy of glycopyrronium bromide.

- Short-acting bronchodilators, as necessary, should be the initial empirical treatment for the relief of breathlessness and exercise limitation.
- In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required, offer the following as maintenance therapy:
  - if FEV_1 is at least 50% predicted: either long-acting $beta_2$ agonist (LABA) or long-acting muscarinic antagonist (LAMA)
  - if FEV_1 is less than 50% predicted: either LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or LAMA.
- In people with stable COPD and an FEV_1 of at least 50% who remain breathless or have exacerbations despite maintenance therapy with a LABA:
  - consider LABA+ICS in a combination inhaler
  - consider LAMA in addition to LABA where ICS is declined or not tolerated.
- Offer LAMA in addition to LABA+ICS to people with COPD who remain breathless or have exacerbations despite taking LABA+ICS, irrespective of their FEV_1.
- Consider LABA+ICS in a combination inhaler in addition to LAMA for people with stable COPD who remain breathless or have exacerbations despite maintenance therapy with LAMA irrespective of their FEV_1.

- The choice of drug(s) should take into account the person's symptomatic response and preference, and the drug's potential to reduce exacerbations, its side effects and cost.

See the NICE pathway on COPD for more information.

[1] National Institute for Health and Clinical Excellence (2010) Chronic obstructive pulmonary disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). NICE clinical guideline 101

[2] NHS Information Centre (2011) QOF prevalence data tables 2010/11

[3] NHS Information Centre. HESonline. Inpatient statistics, primary diagnosis: 3 character 2010–11

Product overview

Drug action

Glycopyrronium bromide (Seebri Breezhaler) is an inhaled LAMA administered using a single-dose dry powder inhaler (the Breezhaler)[4].

New therapeutic indication

Glycopyrronium bromide received a European marketing authorisation in September 2012 and was launched in the UK in November 2012. It is indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD[4].

Course and cost

The recommended dosage of glycopyrronium bromide is inhalation of the powder content of 1 capsule each day. Each hard capsule contains 63 micrograms of glycopyrronium bromide equivalent to 50 micrograms of glycopyrronium. Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 55 micrograms of glycopyrronium bromide equivalent to 44 micrograms of glycopyrronium[4].

Glycopyrronium bromide is available in 30-day and 6-day packs, each including a Breezhaler. The current NHS cost is £27.50 for a 30-capsule pack (1 month of treatment) and £5.50 for a 6-capsule pack (excluding VAT; costs taken from MIMS, December 2012). Based on this, the cost per patient per year is estimated to be £330.

[4] Novartis Pharmaceuticals UK Ltd (2012) Seebri Breezhaler summary of product characteristics

Evidence review

This evidence review is based on 2 phase III studies with similar designs: GLOW1 and GLOW2 (see tables 2 and 3).

GLOW1(D'Urzo et al. 2011)andGLOW2 (Kerwin et al. 2012)

- Design: randomised, double-blind, placebo-controlled trials.
- Population: adults aged 40 years and over with stable moderate to severe COPD (post-bronchodilator FEV_1 30–79% predicted and FEV_1/FVC less than 0.7) and a smoking history of at least 10 pack-years. Patients with a history of asthma were excluded, but no limits on airway reversibility were used. GLOW1 and GLOW2 included 822 and 1066 patients respectively. Long-acting bronchodilators were stopped but ICS and short-acting $beta_2$ agonists could be continued throughout the study. Approximately half of the patients in each group were using ICS at baseline, 59.6% were ex-smokers, and the overall mean smoking history was 47.6 pack-years. The mean post-bronchodilator % predicted FEV_1 was 55.5%[5].
- Intervention and comparison: following a screening and 2 week run-in period, patients were randomised to glycopyrronium bromide 50 micrograms once daily or placebo using a single-dose dry powder inhaler (Breezhaler). GLOW2 also included an open-label tiotropium arm (18 micrograms daily delivered using the Handihaler). The duration of treatment was 26 weeks in GLOW1 and 52 weeks in GLOW2.
- Outcome: the primary outcome measure was trough FEV_1 at week 12. Key secondary outcomes were breathlessness measured using the Transition Dyspnoea Index (TDI; week 26 in both studies) and health status measured using the St George's Respiratory Questionnaire (SGRQ; week 26 in GLOW1 and week 52 in GLOW2).

Table 2 Summary of the GLOW1 study: D'Urzo et al. 2011[6]

	Glycopyrronium bromide 50 micrograms	Placebo	Analysis
Randomised	n=552	n=270	

Efficacy (full analysis population)[a]	n=534	n=260	
Primary outcome: trough FEV_1 at week 12 (LS mean [±SE])	1408±105 L	1301±137 L	Difference 108±14.8 ml (p<0.001)
Selected secondary outcomes:			
TDI focal score at week 26 (LS mean [±SE])	1.84±0.257	0.80±0.294	Difference 1.04±0.235 (p<0.001)
SGRQ score at week 26 (LS mean [±SE])	39.50±0.813	42.31±0.992	Difference −2.81±0.961 (p=0.004)
Safety[b]	n=550	n=267	
Patients reporting serious adverse events	8.4% (46/550)	9.0% (24/267)	Significance of difference vs. placebo not given
Discontinuations due to adverse events	5.8% (32/550)	7.1% (19/267)	Significance of difference vs. placebo not given
Abbreviations: FEV_1, forced expired volume in 1 second; LS, least square; SE, standard error; SGRQ, St. George's Respiratory Questionnaire; TDI, Transition Dyspnoea Index. [a] All randomised patients who took at least 1 dose of study treatment. [b] Patients who took 1 dose of study drug, regardless of whether they were randomised.			

Table 3 Summary of the GLOW2 study: Kerwin et al. 2012[7]

	Glycopyrronium bromide 50 micrograms	Placebo	Tiotropium 18 micrograms	Analysis
Randomised	n=529	n=269	n=268	
Efficacy (full analysis population)[a]	n=525	n=268	n=267	

Primary outcome: trough FEV_1 at week 12 (LS mean [±SE])	1469±141 ml[b]	1372±173 ml[b]	1455±170 ml[b]	Glycopyrronium bromide vs. placebo Difference 97±16.7 ml (p<0.001) Tiotropium vs. placebo Difference 83±19.3 ml (p<0.001) Glycopyrronium bromide vs. tiotropium No significant difference
Selected secondary outcomes:				
TDI focal score at week 26 (LS mean [±SE])	2.13±0.240[b]	1.32±0.289[b]	2.26±0.281[b]	Glycopyrronium bromide vs. placebo Difference 0.81±0.260 (p=0.002)[b] Tiotropium vs. placebo Difference 0.94±0.297 (p=0.002)[b] Glycopyrronium bromide vs. tiotropium No significant difference

SGRQ score at week 52 (LS mean [±SE])	40.85±0.854[b]	44.16±1.040[b]	41.32±1.024[b]	Glycopyrronium bromide vs. placebo Difference -3.32±1.004 (p<0.001)[b] Tiotropium vs. placebo Difference −2.84±1.155 (p=0.014)[b] Glycopyrronium bromide vs. tiotropium No significant difference
Safety[c]	n=525	n=268	n=267	
Patients reporting serious adverse events	12.6% (66/525)	16.0% (43/268)	15.4% (41/267)	Significance of difference vs. placebo/tiotropium not given
Discontinuations due to adverse events	8.0% (42/525)	11.6% (31/268)	7.5% (20/267)	Significance of difference vs. placebo/tiotropium not given

Abbreviations: FEV_1, forced expired volume in 1 second; LS, least square; SE, standard error; SGRQ, St. George's Respiratory Questionnaire; TDI, Transition Dyspnoea Index.

[a] All randomised patients who took at least 1 dose of study treatment.

[b] European Medicines Agency (2012) European public assessment report: Seebri Breezhaler

[c] Patients who took 1 dose of study drug, regardless of whether they were randomised.

Clinical effectiveness

The results of both studies are consistent and show statistically significant improvements in most outcome measures with glycopyrronium bromide, compared with placebo. The absolute difference

in least square mean 12-week trough FEV_1 was 108 ml in GLOW1 and 97 ml in GLOW2 with glycopyrronium bromide compared with placebo ($p<0.001$ in both studies). These differences are around the value which is considered to be the minimum clinically important improvement in trough FEV_1 (100 ml)[8]. In GLOW2, at week 12 the increase in trough FEV_1 compared with placebo was 83 ml for tiotropium.

Statistically significant improvements in breathlessness and health status were seen with glycopyrronium bromide compared with placebo in both studies. However, the differences were not all clinically significant. At week 26, the difference in absolute TDI focal score value was 1.04 in GLOW1 and 0.81 in GLOW2 for glycopyrronium bromide compared with placebo. For tiotropium the difference in absolute TDI focal score after 26 weeks was 0.94 compared with placebo in GLOW2. The minimum clinically important improvement in TDI score (on a scale that ranges from −9 to 9) is considered to be 1[5].

The difference between glycopyrronium bromide and placebo in SGRQ total score was −2.81 at week 26 in GLOW1 and −3.32 at week 52 in GLOW2. In GLOW2, the difference between tiotropium and placebo was -2.84 at week 52. The minimum clinically important improvement in SGRQ total score (on a 100-point scale) is −4[5].

In GLOW2, there was no statistically significant difference between tiotropium and glycopyrronium bromide for any of these outcomes.

Both studies showed a statistically significant decrease in the risk of moderate or severe COPD exacerbations in terms of time to first exacerbation in patients treated with glycopyrronium bromide compared with placebo (GLOW1: hazard ratio [HR] 0.69, 95% confidence interval [CI] 0.50 to 0.95, p=0.023; GLOW2: HR 0.66, 95% CI 0.52 to 0.85, p=0.001). Improvements were also seen with glycopyrronium bromide in terms of use of rescue medication in both studies (difference compared with placebo GLOW1: 0.46 puffs per day, p=0.005; GLOW2: 0.37 puffs per day, p=0.039).

Safety

The percentage of patients reporting adverse events was similar between groups in both studies. Anticholinergic adverse events were most commonly seen. However, for most of these the incidences in excess of placebo were low. According to the summary of product characteristics, the most common anticholinergic adverse reaction reported with glycopyrronium bromide in studies was dry mouth (2.4%). Gastrointestinal effects including gastroenteritis and dyspepsia were also

observed, as were adverse reactions related to local tolerability such as throat irritation, nasopharyngitis, rhinitis and sinusitis[9].

In their assessment of glycopyrronium bromide, the European Medicines Agency (EMA) found that atrial fibrillation was reported more frequently with glycopyrronium bromide compared with placebo. However, when they considered adjudicated electrocardiogram (ECG) recordings, the number of patients with a new or worsening ECG finding of atrial fibrillation was similar for glycopyrronium bromide and placebo. Nevertheless, information on atrial fibrillation has been included in the summary of product characteristics and the EMA has advised that cardiovascular outcomes should be monitored closely post marketing[5].

Evidence strengths and limitations

Although these 2 phase III studies were well conducted, they had some limitations. In their assessment of glycopyrronium bromide, the EMA noted that the most robust clinical criteria were not used to exclude patients suspected of having asthma. Nevertheless, the inclusion and exclusion criteria were considered sufficient to ensure that study participants reflect a general population of patients with moderate to severe COPD[5].

There was also a 2-week run-in phase, after which 38% of patients were excluded in GLOW1 and 47% of patients were excluded in GLOW2, primarily because of failure to meet the diagnostic or severity criteria. In addition, 19% of patients in GLOW1 and 24% of patients in GLOW2 did not complete the studies. The most frequent reasons for this were withdrawal of consent and adverse events[5]. For both studies allocation concealment was unclear, which may have introduced bias.

The majority of patients in these studies had moderate COPD (about 61% in GLOW1 and 64% in GLOW2); no published data are available on patients with mild or very severe disease. Caution is needed when translating phase III trial results to clinical practice in a diverse population of people with COPD.

It is not yet known whether the effects of glycopyrronium bromide are maintained beyond 1 year. Also, more robust evidence comparing glycopyrronium bromide with other active treatments for COPD, such as a LAMA or a LABA (with or without an ICS), would enable its place in therapy to be more clearly established. In GLOW2, glycopyrronium bromide and open-label tiotropium were found to be of similar efficacy. However, the inability to blind tiotropium treatment means these results could be biased. It is difficult to blind tiotropium in clinical trials because the commercial capsules (marked with a logo) contain a hygroscopic powder that cannot be removed and repackaged into unmarked capsules.

The long-term safety of glycopyrronium bromide is still unclear. In view of the potential risk of adverse cardiovascular outcomes related to the mechanism of action of anticholinergic quaternary ammonium compounds and the concerns on cardiovascular safety of same class products[10], the Committee for Medicinal Products for Human Use (CHMP) recommended that adverse cardiovascular outcomes should be followed closely in the post-marketing setting. They also requested a post-authorisation safety study to monitor cardiovascular and cerebrovascular outcomes post-marketing[5].

[5] European Medicines Agency (2012) European public assessment report: Seebri Breezhaler

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

[7] Kerwin E, Hébert J, Gallagher N et al. (2012) Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. European Respiratory Journal 40: 1106–14

[8] National Institute for Health and Clinical Excellence (2010) Chronic obstructive pulmonary disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update)

[9] Novartis Pharmaceuticals UK Ltd (2012) Seebri Breezhaler summary of product characteristics

[10] MHRA (2010) Drug Safety Update

Context

Treatment alternatives

In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, maintenance therapy can be provided by the following (alone or in combination, with choice depending on several factors, see the NICE clinical guideline on COPD for details):

- a LABA
- a LAMA
- a LABA and an ICS in a combination inhaler.

Costs of treatment alternatives

Drug	Usual dosage[a,b]	30-day cost excluding VAT
Glycopyrronium bromide (Seebri Breezhaler)	50 micrograms once daily	£27.50[c]
Aclidinium bromide (Eklira Genuair)	322 micrograms twice daily	£28.60[c]
Tiotropium (Spiriva HandiHaler)	18 micrograms daily	£34.87 (refill £33.50)[d]
Tiotropium (Spiriva Respimat)	5 micrograms daily	£35.50[c]
Formoterol (Formoterol Easyhaler, Atimos Modulite, Foradil, Oxis Turbohaler)	12 micrograms twice daily	£11.88 to £24.80[c,d]
Salmeterol (Serevent Accuhaler, Serevent Evohaler, Neovent)	50 micrograms twice daily	£29.26[c,d]
Indacaterol (Onbrez Breezhaler)	150 micrograms daily	£29.26[d]

[a] Doses taken from the relevant summary of product characteristics.

[b] The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.

[c] Costs taken from MIMS December 2012.

[d] Costs taken from Drug Tariff December 2012.

Estimated impact for the NHS

Likely place in therapy

The choice of treatment for a person with COPD depends on drug efficacy, tolerability to treatment, possible adverse events and the suitability of different inhaler devices to the person. Inhaled long-acting bronchodilators have an important role to play in managing COPD.

Published trial data for the alternative maintenance treatments, LABAs and the established LAMA tiotropium, show they significantly reduce the risk of patient-orientated outcomes, such as COPD

exacerbations[11]. Similar data from clinical outcome trials comparing glycopyrronium bromide (and the other recently marketed LAMA, aclidinium bromide) with active comparators are needed for local decision makers to be able to determine their place in therapy.

Glycopyrronium bromide is less expensive than tiotropium and aclidinium bromide, at £27.50 for 30 days treatment, compared with between £33.50 and £35.50 for tiotropium and £28.60 for aclidinium bromide. Glycopyrronium bromide and tiotropium are administered once daily, compared with twice daily for aclidinium bromide. Although the once-daily dose has demonstrated efficacy, the EMA highlighted a dose-finding study of glycopyrronium bromide that seemed to suggest that a twice-daily regimen could be more effective for this drug. The CHMP has requested a post-authorisation clinical study to further characterise the optimal dosing schedule[12].

Estimated usage

It is difficult to provide estimated usage based on the available data. However, during the financial year 2011–2012, over 4 million items of tiotropium were prescribed in primary care in England, at a cost of nearly £155 million.[13] The manufacturer estimates that glycopyrronium bromide will make up 1.3% of total LAMA usage in the UK in 2013, rising to 6.7% by 2017.

[11] Chong J, Karner C, Poole P (2012) Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews issue 9: CD009157

[12] European Medicines Agency (2012) European public assessment report: Seebri Breezhaler

[13] NHS Business Services Authority: personal communication December 2012

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

For information about the process used to develop this evidence summary, see Evidence summaries: new medicines – interim process statement.

Contact NICE

National Institute for Health and Clinical Excellence
Level 1A, City Tower, Piccadilly Plaza, Manchester M1 4BT

www.nice.org.uk; nice@nice.org.uk; 0845 033 7780