General Commissioning Policy

Treatment	Glycopyrronium bromide (Seebri Breezhaler, Novartis)
For the treatment of	It is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Background	Glycopyrronium bromide (Seebri Breezhaler) is a once daily LAMA for maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. Alternative treatment options are Tiotropium spinhaler/ Respimat which is given once daily and aclidinium guanair which is given twice daily.
Commissioning position	Glycopyrronium bromide inhaler is not routinely commissioned for use in its licensed indication for COPD
Effective from	December 2012
Summary of evidence / rationale	Chronic obstructive pulmonary disease is characterised by airflow obstruction that is usually progressive, not fully reversible, and does not change markedly over several months. The main goals of treatment are to prevent and control symptoms, reduce frequency and severity of exacerbations, improve health status, and increase exercise tolerance. Glycopyrronium bromide is an inhaled long-acting muscarinic antagonist (LAMA) for maintenance bronchodilator treatment of COPD. **NICE guidance clinical guideline 101: COPD 2010** http://guidance.nice.org.uk/CG101/NICEGuidance This guidance recommends that for patients with stable COPD, who remain breathless or have exacerbations despite use of a short-acting bronchodilator as required, the following may be considered: • FEV1 ≥50% of predicted, either a LAMA or LABA. • FEV1<50% of predicted, either a LABA in combination with an inhaled steroid, or a LAMA. LABA plus a LAMA if an ICS cannot be tolerated. NICE does not make specific reference to individual drugs but at present the only other licensed LAMA available is tiotropium but there is now aclidinium also recently licensed. **Scottish Medicines Consortium December 2012** Was accepted for use as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD) http://www.scottishmedicines.org.uk/General/Homepage_Search_Results?q=glycopyrronium **RDTC New drug evaluation: Glycopyrronium Bromide for COPD; November 2012** http://www.nyrdtc.nhs.uk/docs/nde/NDE_119_Glycopyrronium.pdf **MTRAC guidance: Glycopyrronium bromide (Seebri Breezhaler); November 2012** ➢ Based on the published evidence, glycopyrronium bromide appears to

Notes

1. This Policy will be reviewed in the light of new evidence, or guidance from NICE.
2. General Commissioning Policies are agreed by the Planning and Commissioning Committee on behalf of NHS Hull CCG.

be of similar efficacy to tiotropium but longer term data are lacking.

- Based on current prices, glycopyrronium bromide is less expensive than tiotropium.
- Glycopyrronium bromide could be considered as an option when initiating treatment for a new patient.
- There is insufficient evidence to support a switch in prescribing from tiotropium to glycopyrronium bromide in patients already receiving treatment for chronic obstructive pulmonary disease (COPD).
- The patent for tiotropium is expected to expire in 2015.
- Commissioners may also wish to consider the prescribing of glycopyrronium and tiotropium within the context of the development of an overall care pathway for COPD treatment.

Clinical Trials

Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: the GLOW1 trial
D'Urzo et al.
Respiratory Research 2011 Dec. 7,12;156: 1-13

This was a Phase III randomised double blind trial to evaluate the efficacy, safety and tolerability of once daily glycopyrronium bromide compared with placebo in patients with moderate-to-severe COPD.
Patients with moderate-to-severe COPD (as defined in the 2008 GOLD guidelines) were eligible if they were >40 years of age, had a smoking history of >10 pack-years, post-bronchodilator forced expiratory volume in 1 second (FEV1) of <80% and .30% of predicted normal value and post-bronchodilator FEV1/FVC ratio of <0.7. exclusion criteria included lower respiratory tract infection within 6 weeks, concomitant pulmonary disease, history of asthma, lung cancer or long QT syndrome, symptomatic prostatic hyperplasia, bladder-neck obstruction, moderate/severe renal impairment, urinary retention, narrow-angle glaucoma and history of alpha-1 antitrypsin deficiency. Patients were also excluded if they were participating in a supervised pulmonary rehab programme, had contraindications for tiotropium or ipratropium or had experienced adverse reactions to inhaled anticholinergic.
Patients were randomised in a 2:1 ratio to 26 weeks treatment with glycopyrronium once daily or placebo. Inhaled corticosteroids were allowed but LABAs were not.
The primary outcome measure was trough FEV1 at week 12. Secondary outcomes were breathlessness on the transition dyspnoea index (TDI) and health-related quality of life according to the SGRQ at week 26, time to first moderate or severe COPD exacerbation and mean daily rescue medication use over 26 weeks.

Glycopyrronium (n=550)	Placebo (n=267)
Trough FEV1 at 12 weeks (litres)	
1.408 +/-0.0105	1.301 +/- 0.0137
Treatment difference 108 +/- 14.8ml, p<0.001	
TDI at week 26	
1.84	0.80
Treatment difference 1.04 (1 point difference is considered clinically meaningful)	
SGRQ	
39.5	42.31
Treatment difference	

-2.81, p=0.004
Reduction in risk of exacerbation (time to first exacerbation)
-31% compared to placebo (HR 0.69, 95% CI: 0.5 to 0.949) p=0.02

The incidence of adverse events was lower in patients receiving glycopyrronium (57.5% of patients), compared with placebo (65.2%), largely due to a higher frequency of COPD worsening in placebo group. Other adverse events, including those typically associated with anticholinergics (GI disturbances, urinary difficulty, urinary retention, dry mouth), occurred at low frequencies in both groups.

Efficacy and safety of NVA237 versus placebo and tiotropium in patients with moderate-to-severe COPD over 52 weeks; The GLOW2 study.
E.Kerwin et al.
Eur. Respiratory Journal. 2012; Nov; 40(5): 1106-14.

The inclusion and exclusion criteria for this trial was the same as GLOW1 as was the primary and secondary outcomes. This was a multicentre, double-blind, placebo-controlled with open-label tiotropium arm, parallel group study. Patients were randomised to glycopyrronium, placebo or tiotropium (handihaler device) in a ratio of 2:1:1 for a period of 52 weeks.
A total of 1066 patients were randomised to one of the three treatment groups.
Results showed significantly higher trough FEV1 at week 12 for patients receiving both glycopyrronium and tiotropium compared to placebo ($p<0.001$). The study was not designed to compare glycopyrronium directly to tiotropium. Glycopyrronium significantly improved TDI score at 26 weeks compared with placebo, with a treatment difference of 0.81 (95% CI: 0.299 to 1.320, p=0.002). This improvement in TDI seen with glycopyrronium was comparable to that seen in those receiving tiotropium (treatment difference vs. placebo: 0.94, 95% CI: 0.356 to 1.521, p=0.002). SGRQ score at week 52 was significantly improved in patients receiving glycopyrronium, with a treatment difference vs. placebo of -3.32 (95% CI: -5.287 to -1.346, $p<0.001$). Over 52 weeks, glycopyrronium reduced the risk of exacerbations in terms of time to first moderate or severe exacerbation by 34% compared to those receiving placebo (HR: 0.66, 95% CI: 0.52 to 0.85, p=0.001). This compares to a reduction in risk of 39% vs. placebo in those receiving tiotropium. A 35% reduction in rate of moderate or severe exacerbations was seen with glycopyrronium compared to placebo (0.54 exacerbations per year vs. 0.80, rate ratio: 0.66, 95% CI: 0.496 to 0.869, p=0.003). Glycopyrronium provided rapid bronchodilation following the first dose on day one, with significantly higher FEV1 at all time points (from five minutes to four hours post-dosing), compared with placebo ($p<0.001$) and tiotropium ($p<0.01$). However, this was not a pre-specified endpoint. Both glycopyrronium and tiotropium were shown to be superior to placebo in reducing the rate of moderate exacerbations which required antibiotics or oral corticosteroids.

Once-daily NVA237 improves exercise tolerance from the first dose in patients with COPD: the GLOW3 trial
Beeh KM et al
International Journal of COPD 2012: 7 503-513.
Patients were enrolled into this trial with FEV1 <80% to >40% of their predicted normal volume. This was a multicenter trial; patients were

	randomised within a cross-over design into two treatment arms: once daily glycopyrronium followed by placebo or placebo followed by glycopyrronium for 3 weeks, with a 14 day wash out period. The primary outcome measure was the effect of glycopyrronium on exercise tolerance vs. placebo after three weeks of treatment. On days one and 21, exercise tolerance was measured by tolerance time during submaximal exercise testing (SMET). SMET was performed at 80% of a patients' maximum working capacity evaluated at screening. Glycopyrronium was significantly superior to placebo with respect to exercise tolerance time at day 21. The difference between the treatment groups at day 21 was 88.9 seconds, approximately a 21% difference ($p<0.001$). The minimal important difference for SMET is 1.25 minutes, so this change is considered to be clinically important.5 At day 21, the treatment difference in trough FEV1 (a secondary variable) between glycopyrronium and placebo was no different from baseline.
Date	December 2012
Policy to be reviewed by	December 2014
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