Glycopyrronium bromide (Seebri) for chronic obstructive pulmonary disease (GLY-co-pi-RO-ni-um)

KEY POINTS

Once-daily dosing provides symptomatic control for some people with COPD
Glycopyrronium (Seebri Breezhaler) once daily provides maintenance bronchodilation lasting for 24 hours in patients with COPD.

Safety profile and symptom control similar to those of tiotropium
Glycopyrronium provides similar improvements in lung function and symptom control to those of tiotropium, with a similar safety profile.

As with tiotropium, not all patients will achieve a clinically relevant benefit from glycopyrronium treatment
Conduct a therapeutic trial of any long-acting bronchodilator to determine effectiveness in improving symptoms in the individual patient.

Use with caution in people with risk factors for angle-closure glaucoma or prostatic symptoms
Acute angle-closure crisis and urinary retention are known adverse effects associated with anticholinergics. Advise patients to be alert to symptoms indicating these conditions.

PBS listing
Restricted benefit
Glycopyrronium bromide (Seebri) is PBS listed as a Restricted Benefit for treatment of chronic obstructive pulmonary disease.

May be prescribed by nurse practitioners within collaborative arrangements
Authorised nurse practitioners may prescribe this medicine on the PBS. See the PBS website for more information on nurse practitioner PBS prescribing.

Who is it for?
Glycopyrronium is for maintenance bronchodilator treatment of airflow limitation in patients with COPD.

Do not use in people with acute exacerbation of COPD
Glycopyrronium is indicated for long-term maintenance treatment and is not indicated for acute exacerbations of COPD (i.e. as a rescue therapy).1

Where does it fit?
Glycopyrronium is PBS listed as a long-acting bronchodilator treatment option in people with COPD and, along with tiotropium, this is the second long-acting anticholinergic listed for COPD.

Maintenance treatment for symptomatic control in COPD
Current clinical management algorithms support regular use of an inhaled long-acting bronchodilator, in conjunction with short-acting ‘rescue’ bronchodilators, in patients with mild to severe COPD.2

What is it?
Glycopyrronium is an inhaled long-acting anticholinergic that produces bronchodilation by blocking the action of acetylcholine on the muscarinic receptors of airway smooth muscle cells.1 It has an onset of action within 5 minutes after inhalation, and duration of effect is sustained over 24 hours.

ADDITIONAL INFORMATION
Nurse practitioner PBS prescribing:
www.pbs.gov.au/browse/nurse

COPD: chronic obstructive pulmonary disease
PBS: Pharmaceutical Benefits Scheme

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Long-acting bronchodilators may also be used in combination with inhaled corticosteroids in severe COPD if repeated exacerbations occur.\(^2,3\)

Aside from the long-acting anticholinergics, other long-acting inhaled bronchodilators for COPD include the long-acting beta\(_2\) agonists (LABAs) and fixed-dose combinations of fluticasone with salmeterol and budesonide with eformoterol.

There is no evidence to support a benefit of one class of long-acting bronchodilators over the other.\(^4\) Therefore, choose a long-acting bronchodilator based on effective symptom control in the individual patient; that is, if there is no clinical response for a particular medicine, discontinue use and try another.

A trial of a bronchodilator may require several weeks.\(^5\) Note that some patients will achieve a symptomatic benefit from regular long-term use despite a lack of measurable improvement in lung function.\(^5\)

If adequate symptom control is not achieved with a single agent, a second long-acting bronchodilator from the other class (either long-acting anticholinergic or LABA) may be added.\(^3\)

Do not co-administer glycopyrronium with other inhaled anticholinergics; combinations with inhaled anticholinergic agents have not been studied. If treating with glycopyrronium, select a short-acting beta\(_2\) agonist (SABA) for rescue therapy instead of ipratropium.\(^1,2\)

Do not use glycopyrronium for relief of acute symptoms. If repeated exacerbations occur with glycopyrronium treatment, consider discontinuing and instead try a LABA for maintenance therapy. In more severe cases, addition of a LABA to the long-acting anticholinergic or use of a LABA/ICS combination may be required if exacerbations continue.\(^2,3\)

**How does it compare?**

Efficacy and safety of glycopyrronium 50 micrograms once daily for COPD have been demonstrated in three multicentre, randomised, double-blind placebo-controlled trials — GLOW1, GLOW2 and GLOW5 — which ran over 26 weeks, 52 weeks and 12 weeks, respectively.\(^6,7\)

In GLOW1, 822 patients were randomised to receive glycopyrronium or placebo.

GLOW2 (n = 1066) included an additional open-label treatment arm in which patients were randomised to receive 18 micrograms of tiotropium once daily.

GLOW5 (n = 657) was a parallel-group study directly comparing safety and efficacy of glycopyrronium with those of tiotropium.

The primary outcome in all studies was improvement in lung function as indicated by spirometric measurement of trough FEV\(_1\) (FEV\(_1\) measurement before the daily dose, i.e. 23 hours after the previous dose) at week 12. Several secondary symptomatic endpoints were also measured.

People ≥ 40 years of age with moderate to severe COPD\(^*\) and with a smoking history (current and ex-smokers) of ≥ 10 pack-years\(^†\) were eligible for inclusion in the GLOW trials. People who had never smoked were excluded from the trial population.

All patients were provided with salbutamol as rescue medication for use as required.

Also excluded from the trial population were people with:

- asthma
- lung cancer
- clinically significant cardiovascular disease (such as ischaemic heart disease, MI, arrhythmia or long-QT syndrome)
- symptomatic prostatic hyperplasia
- bladder-neck obstruction
- moderate to severe renal impairment
- urinary retention
- angle-closure glaucoma
- a known history of alpha-1 antitrypsin deficiency.

It should be noted that the number and nature of conditions excluded suggest that the trial population may not be reflective of the Australian COPD population.

**Glycopyrronium improves lung function in COPD**

Spirometry at 12 weeks showed that glycopyrronium significantly improved mean trough FEV\(_1\) by 108 mL and 97 mL compared with placebo (p < 0.001) in GLOW1 and GLOW2, respectively.
EVIDENCE SNAPSHOT

WHAT IS KNOWN ABOUT THIS DRUG?

Glycopyrronium is a long-acting anticholinergic bronchodilator providing similar levels of symptom control for people with COPD, and with a similar adverse-effect profile, to those of tiotropium.

AREAS OF UNCERTAINTY

The long-term clinical effects of glycopyrronium are unknown, as there are no data beyond use for 64 weeks.

While head-to-head data for glycopyrronium versus tiotropium are available, there are no published studies to establish non-inferiority of glycopyrronium relative to LABAs in treatment of COPD.

WHAT DOES NPS SAY?

Glycopyrronium provides an alternative to tiotropium as a long-acting anticholinergic for once-daily use in maintenance treatment for people with COPD.

It provides symptomatic control in COPD similar to that of once-daily tiotropium, with a comparable profile and rate of adverse effects.

As with tiotropium, improvements in lung function and symptom control with glycopyrronium treatment vary between patients. For a patient with COPD, choose the maintenance therapy that provides the best relief of symptoms. This may require trying a number of options to find the optimal regimen.

Glycopyrronium is not indicated for the initial treatment of acute exacerbations of COPD, i.e. as rescue therapy. Do not prescribe glycopyrronium to be used concomitantly with other inhaled anticholinergics (ipratropium, tiotropium).

ADDITIONAL INFORMATION

Making sense of equivalence and non-inferiority trials: www.australianprescriber.com/magazine/36/5/170/3

The improvement in FEV₁ was observed for glycopyrronium versus placebo from day 1 and maintained over all time points (up to 26 weeks in GLOW1 and 52 weeks in GLOW2).³,⁷

An improvement in trough FEV₁ of 100 mL is considered to be clinically meaningful and a level that can be perceived by patients.³ This suggests that some trial patients receiving treatment did not reach a clinically meaningful improvement in lung function.

Glycopyrronium has efficacy comparable to that of tiotropium

The GLOWS study used a double-dummy design so that patients and dispensing clinicians were blinded to treatment with glycopyrronium, tiotropium or their respective placebos.⁷

The primary efficacy objective of the study was to demonstrate the non-inferiority of glycopyrronium to tiotropium in terms of trough FEV₁ at 12 weeks.

A secondary efficacy objective was to show superiority of glycopyrronium over tiotropium, in the event that the non-inferiority criterion was met.

In the per-protocol set of patients (which excluded patients who deviated from the treatment protocol to which they were randomised), there was no significant difference in trough FEV₁ for glycopyrronium and tiotropium (i.e. no treatment difference, p < 0.01).

Thus, glycopyrronium was found to be non-inferior to tiotropium at 12 weeks. However, as the difference in trough FEV₁ for the two treatments was not statistically significant, glycopyrronium was not shown to be superior to tiotropium.

Effectiveness of glycopyrronium comparable to that of tiotropium up to 52 weeks

In the 52-week GLOW2 study, 1066 patients with moderate to severe COPD were randomised to receive glycopyrronium, open-label tiotropium or placebo in a 2:1:1 ratio.
Glycopyrronium and tiotropium showed comparable improvements in lung function over placebo at 12, 26 and 52 weeks. Improvements in trough FEV₁ at 12 weeks for glycopyrronium versus placebo and tiotropium versus placebo were 97 mL and 83 mL, respectively (both p < 0.001). These results are similar to the mean improvements from baseline reported in GLOW5 for glycopyrronium (103 mL) and tiotropium (99 mL) at 12 weeks and should be considered in light of the 100 mL threshold regarded as clinically meaningful.

**Glycopyrronium treatment shows improvements in symptomatic endpoints**

Symptomatic (secondary) endpoints investigated in the GLOW studies included:

- breathlessness, as measured using the transition dyspnoea index (TDI)
- overall health status, as measured using the St George’s Respiratory Questionnaire (SGRQ)
- time to first exacerbation and frequency of rescue medication use.

At week 26, results for these endpoints were comparable between glycopyrronium and tiotropium. The TDI measures the severity of dyspnoea in terms of:

- functional impairment (impact of breathlessness on the ability to carry out a task)
- magnitude of a task (the types of tasks that causes breathlessness)
- magnitude of effort (level of effort resulting in breathlessness).

In GLOW5, the difference in improvement in TDI score between glycopyrronium and tiotropium at 12 weeks was not statistically significant; that is, both treatments provided a comparable improvement in breathlessness. In both treatment groups, 58.6% of patients achieved an improvement in TDI score considered clinically relevant.

In GLOW2, at 26 weeks both glycopyrronium and tiotropium moderately increased the percentage of patients achieving a clinically relevant improvement in TDI (55.3% [p = 0.01] and 53.4% [p = 0.032], respectively, compared with placebo [44.2%]).

However, in a pooled analysis of the GLOW1 and GLOW2 data, glycopyrronium fell short of the threshold for a clinically relevant improvement in TDI score, which was achieved with tiotropium, although the difference between the treatments was not statistically significant. Neither glycopyrronium nor tiotropium showed a clinically relevant difference in TDI at 52 weeks.

The SGRQ is a 50-item questionnaire that measures the impact of COPD on quality of life in terms of symptoms, activity and psychosocial effects. In GLOW5 the difference in SGRQ scores for glycopyrronium and tiotropium at week 12 was not statistically significant: 55.2% and 54% of patients treated with glycopyrronium and tiotropium, respectively, achieved a clinically relevant improvement in SGRQ score.

In a pooled analysis of data from GLOW1 and GLOW2, on average neither glycopyrronium nor tiotropium achieved the SGRQ threshold for clinical relevance. However, 57.8% (p < 0.001) and 61% (p < 0.05) of patients using glycopyrronium or tiotropium, respectively, did achieve a clinically relevant improvement compared with 47.6% for patients receiving placebo.

In GLOW5 and in a pooled analysis of GLOW1 and GLOW2 data, both glycopyrronium and tiotropium were comparable in delaying patients’ first moderate or severe exacerbation and in their use of rescue medication.

**Limited comparative data with other long-acting bronchodilators**

In a randomised, double-blind 26-week trial in patients with moderate to severe COPD (n = 2144) dual bronchodilation therapy was compared with placebo as well as treatment control arms given glycopyrronium, open-label tiotropium, or indacaterol. Improvement in trough FEV₁ at 26 weeks compared with placebo (primary endpoint) was comparable in the glycopyrronium, tiotropium and indacaterol arms.

A meta-analysis of 40 randomised controlled studies evaluated comparative efficacy of glycopyrronium, tiotropium, indacaterol, salmeterol or eformoterol versus placebo. Indacaterol was associated with a higher trough FEV₁ and greater improvement in SGRQ score compared with other treatments, followed by glycopyrronium and tiotropium, which had comparable results.
However in the absence of head-to-head studies, no firm conclusions can be drawn about their relative efficacy.14

**Safety issues**

The most commonly reported adverse events in the GLOW studies were generally consistent with complications of COPD, and use of anticholinergics.6,7,10,12 Local adverse effects due to drug delivery may include throat irritation, nasopharyngitis, rhinitis and sinusitis.1

There are no safety data beyond 64 weeks of treatment.15

**Adverse effects similar to those of other anticholinergics**

In the pivotal trials the safety profiles of glycopyrronium and tiotropium were similar, with dry mouth occurring more frequently for glycopyrronium (2.2%) than for tiotropium (1.5%). Gastrointestinal effects and urinary retention often associated with anticholinergics were infrequent and occurred no more frequently with glycopyrronium than with tiotropium.6,7,12

In GLOW2, UTI occurred less frequently for glycopyrronium (1.8%) than for tiotropium (3.8%).7

**Caution required in people with risk factors for angle-closure glaucoma**

People with risk factors for angle-closure glaucoma (e.g. Asian ethnicity, small eye, narrow angle of anterior chamber, shallow anterior chamber, long sight) can in rare cases experience acute angle-closure crisis precipitated by use of anticholinergics.16 People with angle-closure glaucoma were excluded from the pivotal trials.

Advise patients to be alert to signs of an acute angle-closure crisis (e.g. redness of the eye, eye pain, blurring of vision or visual halos), and to stop treatment and seek medical advice if these symptoms occur.1

**Caution required in people with prostatic symptoms**

Urinary retention occurs infrequently with use of anticholinergics;16 patients with prostatic symptoms were excluded from the pivotal trials.1

Advise patients to stop treatment and seek medical advice if they experience pain or difficulty passing urine.

**Caution required in people with severe renal impairment**

Inhaled glycopyrronium is primarily renally excreted.1 Administration of glycopyrronium to people with severe renal impairment (eGFR < 30 mL/min/1.73 m²) may result in up to a twofold increase in systemic exposure, increasing the risk of adverse events.

Monitor patients closely for any treatment-emergent adverse events if they have severe renal impairment.

**Older people**

Patients ≥75 years of age were included in the pivotal trials and overall did not experience adverse events more frequently than the younger population.

However, headache and UTI were the most frequent adverse effects in this group, indicating that the older population may be at higher risk of these side effects.1,17

**Be aware of paradoxical bronchospasm**

Paradoxical bronchospasm occurs rarely with any inhalation therapy and may occur with glycopyrronium. If it occurs, stop glycopyrronium and choose an alternative therapy, as described in current clinical management algorithms.2,3

**Consider possible cardiovascular effects**

Cardiovascular effects, including atrial fibrillation, tachycardia and MI, and stroke, may be a concern with long-acting anticholinergic bronchodilators.17–19

In GLOW1 and GLOW2 the incidence of major cardiovascular events was low overall and similar for glycopyrronium and placebo (both 0.4%).12 GLOW5 also reported a low rate of serious cardiovascular events (0.6%) for both glycopyrronium and tiotropium.10

The GLOW studies excluded patients with unstable ischaemic heart disease, left ventricular failure, or a history of MI or long-QT syndrome. Therefore the potential for unwanted cardiovascular effects may be a concern.20

Monitor patients with cardiovascular risk factors closely when prescribing glycopyrronium.

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UTI: urinary tract infection  
eGFR: estimated glomerular filtration rate
For information about reporting adverse reactions to the TGA, or to report suspected adverse reactions online, see the TGA website‡ or use the ‘Blue Card’ distributed with the October issue of Australian Prescriber.

**Reason for PBS listing**

The PBAC recommended listing of inhaled glycopyrronium 50 micrograms once daily on a cost-minimisation basis (i.e. equivalent cost to PBS) compared with tiotropium 18 micrograms once daily.

The PBAC accepted non-inferiority of glycopyrronium to tiotropium as single therapy with regard to efficacy and safety. The PBAC noted a need for further data on use of glycopyrronium in combination with LABA/ICS treatment and requested that the final data from the interim analysis presented in the submission be provided when complete.

**Dosing issues**

The recommended dose of glycopyrronium is one 50 microgram capsule inhaled once daily.

Administration of glycopyrronium requires the use of the Breezhaler inhaler device. Instruct patients in the correct use of this device (described in the Lung Foundation’s COPD Patient Guide§) before prescribing and ensure correct technique during follow-up appointments.

For more information on managing chronic obstructive pulmonary disease, refer to NPS Case study 63 report.§

**Information for patients**

Explain to patients that, as a maintenance treatment, glycopyrronium must be used once daily even if the patient feels well.

Ensure they understand the difference between their maintenance and reliever medicines, and remind them to carry their reliever inhaler at all times.

Explain that glycopyrronium must be taken using the Breezhaler device; it cannot be taken using other devices the patient may use for other inhaled medicines.

Check the patient’s inhaler technique using the Breezhaler device, and direct them to the Lung Foundation’s COPD Patient Guide, which describes the Breezhaler device and others commonly used in treatment of COPD.

Arrange a follow-up appointment with the patient after several weeks to assess whether symptoms are adequately controlled with their current medication.

Tell the patient to seek urgent medical attention if they experience:

- tightness in the chest, wheezing or breathlessness immediately after using the inhaler (symptoms of bronchospasm)
- pain or difficulty passing urine (symptoms of dysuria).

Tell the patient to stop taking glycopyrronium and seek urgent medical attention if they experience symptoms of acute angle-closure crisis such as:

- redness of the eye
- eye pain
- blurring of vision
- visual halos.

If the patient experiences irregular heartbeat they should seek medical care urgently.

REFERENCES


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The information contained in NPS RADAR is derived from a critical analysis of a wide range of authoritative evidence and is current at the time of publication. Any treatment decisions based on the information provided in NPS RADAR should be made in the context of the clinical circumstances of each patient.

NPS RADAR articles may be updated when there is new evidence about safety or efficacy, or in case of regulatory or PBS listing changes.

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