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ADIS DRUG CLINICAL Q&A

Inhaled glycopyrronium bromide: a guide to its use in moderate to severe chronic obstructive pulmonary disease

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Abstract Inhaled glycopyrronium bromide (Seebri® Breezhaler® capsules), a once-daily, long-acting muscarinic receptor antagonist, is indicated as a long-term maintenance bronchodilator for the symptomatic treatment of adults with chronic obstructive pulmonary disease (COPD). In randomized, controlled trials, inhaled glycopyrronium bromide (at a delivered dose of 44 μg) once daily was associated with significantly better improvements in lung function, dyspnoea scores, health status, exacerbation rates and/or exercise endurance time than placebo in patients with moderate to severe COPD, and was generally well tolerated.

Adis evaluation of inhaled glycopyrronium bromide in patients with moderate to severe chronic obstructive pulmonary disease
What are its key clinical benefits?
Administered once daily
Improves lung function, dyspnoea, health status, exacerbation rates and exercise endurance
Low potential for drug interactions
Generally well tolerated
No dosage adjustment required in patients who are elderly
What are its key clinical limitations?
Use with caution in patients with certain cardiovascular conditions, narrow-angle glaucoma or urinary retention
Pharmacoeconomic analyses comparing the cost-effectiveness of glycopyrronium bromide vs. other long-acting bronchodilators are lacking

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What is the rationale for developing the drug?

Chronic obstructive pulmonary disease (COPD) is caused by inflammation in the lung and airways, and generally progressively leads to a variable combination of parenchymal tissue destruction (emphysema) and small airways disease (obstructive bronchiolitis) and, ultimately, chronic limited airflow [1]. Pharmacological therapy for COPD does not alter the course of the disease, but rather aims to reduce symptom severity, decrease the frequency and severity of exacerbations, and improve exercise tolerance and health-related quality-of-life [1].

Bronchodilators play a key role in the management of COPD symptoms, with preference generally given to inhaled long-acting agents, such as long-acting muscarinic receptor antagonists (LAMAs; e.g. glycopyrronium bromide, aclidinium bromide and tiotropium bromide) and long-acting β_2-adrenergic receptor agonists (LABAs; e.g. formoterol, indacaterol and salmeterol) over inhaled short-acting agents or orally administered agents [1].

Patient adherence to COPD therapy is often suboptimal, which may lead to poor clinical outcomes and increased healthcare costs [2, 3]. Although many factors influence adherence to COPD therapy, the use of agents that can be administered once daily may help improve patient adherence [2, 4–7].

One such agent is inhaled glycopyrronium bromide (Seebri® Breezhaler® capsules), which is approved in various countries, including those in the EU [8], as an once-daily maintenance bronchodilator for the symptomatic treatment of adult patients with COPD. Doses of inhaled glycopyrronium bromide reported in this article are for the dose of glycopyrronium delivered by the inhaler (Table 1) [8].

How does the drug work?

Glycopyrronium bromide, a quaternary ammonium compound, is a competitive muscarinic receptor antagonist (also known as an anticholinergic) [8]. When inhaled, it acts locally in the lungs to dilate the airways through the inhibition of acetylcholine-induced constriction in airway smooth muscle cells [8].

Ideally, inhaled bronchodilator agents should have high affinity to block the muscarinic M_3 receptor subtype (which mediates contraction of airway smooth muscle), but low affinity for the M_2 receptor subtype (which are located primarily in the heart) [9, 10]. In vitro, glycopyrronium has a more than fourfold higher selectivity for human M_3 receptors than for human M_2 receptors, and dissociates slower from the M_3 receptor than from the M_2 receptor (dissociation half-life 11.4 vs. 1.07 min) [10, 11].

In vitro [11] and clinical [12, 13] studies have shown that the onset of action is faster with glycopyrronium bromide than with tiotropium bromide. For example, in patients with moderate to severe COPD, values for forced expiratory volume in one second (FEV_1) significantly ($p < 0.05$) favoured inhaled glycopyrronium bromide 44 μg over inhaled tiotropium 18 μg from 5 min to 2 h post-dose on day 1 of a phase II study [12] and at 5 and 15 min post-dose on day 1 of a phase III study [13].

Inhaled glycopyrronium bromide had no relevant effect on the Fridericia-corrected QT interval and other cardiac parameters when administered at a supratherapeutic single dose of 352 μg (i.e. eightfold the daily clinical dose) in a placebo- and positive-controlled study in healthy volunteers [14].

For whom is the drug indicated?

Inhaled glycopyrronium bromide 44 μg is approved as an once-daily, long-term maintenance bronchodilator treatment for the symptomatic control of COPD in adults in the EU [8] and other countries. In the EU [8], the recommended dosage is the contents of one capsule (i.e. glycopyrronium bromide 44 μg) inhaled once daily, and at the same time each day, using the single-dose Seebri® Breezhaler® inhaler. Patients should be instructed on the correct administration of the product [8]. A summary of the EU prescribing information is provided in Table 1.

What is its clinical efficacy in COPD?

The efficacy of inhaled glycopyrronium bromide 44 μg once daily in patients with moderate to severe COPD has been assessed in randomized, double-blind, placebo-controlled, multicentre, phase III trials known as the GLOW (GLycopyrronium bromide in chronic Obstructive pulmonary disease airWays) studies [13, 15, 16].

The pivotal trials were GLOW1 ($n = 882$) [15], which had a duration of 26 weeks and GLOW2 ($n = 1{,}066$) [13], which had a duration of 52 weeks [13]. In these trials, mean patient age was ≈64 years, and 60–65, 34–40 and 0–1.1 % of patients across all treatment groups met the respective Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for moderate, severe or very severe disease [13, 15]. Results for various parameters were generally reported as the least squares mean (LSM) between-group difference (BGD).

Although open-label inhaled tiotropium bromide 18 μg once daily was included as a reference comparator in GLOW2 [13], the study was not powered to show statistical superiority of inhaled glycopyrronium bromide over inhaled tiotropium bromide. Tiotropium bromide was associated with significantly better effects on lung function and other parameters than placebo, with improvement being generally comparable with those with glycopyrronium bromide [13]. Results in the tiotropium bromide treatment arm are not discussed further.

What is its effect on lung function?

In GLOW1 [15] and GLOW2 [13], treatment with inhaled glycopyrronium bromide 44 μg once daily was associated with better lung function than placebo in patients with moderate to severe COPD. The LSM BGD in trough FEV_1 significantly favoured glycopyrronium bromide over placebo at 12 weeks (primary endpoint) [13, 15], as well as at day 1 [13, 15] and weeks 26 [13, 15] and 52 [13] (Table 2). Peak FEV_1 values obtained at the end of day 1 and after 12, 26 and 52 weeks' treatment were also significantly ($p < 0.001$) higher in recipients of glycopyrronium bromide than in recipients of placebo in GLOW2 [13].

Inhaled glycopyrronium bromide had a fast onset of action on day 1, with FEV_1 values obtained at 5 min and at 15 min after administration of study drug being significantly ($p < 0.001$) higher in glycopyrronium bromide than placebo recipients in both GLOW1 [15] and GLOW2 [13].

Where assessed, inspiratory capacity [13, 15] and trough forced vital capacity [13] were also significantly ($p < 0.05$) higher with inhaled glycopyrronium bromide than with placebo at all time points [13, 15] (Table 2).

What is its effect on dyspnoea?

Inhaled glycopyrronium bromide improved symptoms of dyspnoea to a greater extent than placebo, with improvements from baseline in Transition Dyspnoea Index (TDI) focal scores being significantly greater in glycopyrronium

Table 1 Prescribing summary of inhaled glycopyrronium bromide (Seebri® Breezhaler® capsules) in the treatment of chronic obstructive pulmonary disease (COPD) in the EU [8]

What is its approved indication?	
Maintenance bronchodilator treatment to relieve symptoms in adults with COPD	
What is its dosage, availability and storage?	
Route	Inhalation using the Seebri® Breezhaler® inhaler (do not swallow capsules)
Recommended dosage	Contents of one capsule once daily (at the same time each day)
Dose in capsule	63 μg of glycopyrronium bromide equivalent to 50 μg of glycopyrronium
Dose delivered by the inhaler	55 μg glycopyrronium bromide equivalent to 44 μg glycopyrronium
Availability	Packages containing 6, 12 or 30 unit-dose blister-packed capsules plus one inhaler (use the inhaler provided with each new prescription; dispose of inhaler after 30 days of use)
Storage of capsules	Always store in the blister to protect from moisture; remove with dry hands only immediately before administrating the contents of the capsule with the inhaler
What is its pharmacokinetic profile?	
Absorption	Rapidly absorbed into the systemic circulation after inhalation (t_{max} 5 min)
	Absolute bioavailability: 45 % of delivered dose (≈90 % and ≈10 % of systemic exposure via gastrointestinal and lung absorption, respectively)
	Time to steady state: 1 week
Metabolism	Undergoes hydroxylation to form a variety of mono- and bis-hydroxylated metabolites and direct hydrolysis to form a carboxylic acid derivative (M9)
	Oxidative biotransformation appears to involve multiple cytochrome P450 enzymes
Elimination	Predominantly (60–70 %) cleared from the plasma via renal elimination of the parent drug
	Metabolism and, to a lesser extent, biliary clearance account for the remaining (30–40 %) total plasma clearance
	Mean terminal elimination half-life: 33–57 h
What are the contraindications to its use?	
Hypersensitivity to glycopyrronium or any of the excipients (lactose monohydrate; magnesium stearate) in the product	
How should it be used in special populations?	
Elderly patients (aged ≥75 years)	No dosage adjustments are required
Patients with renal impairment	Mild to moderate: no dosage adjustments are required
	Severe or end-stage renal disease requiring dialysis: use only if the expected benefits outweigh the risks (exposure to glycopyrronium may be increased)
Patients with hepatic impairment	No major increase in exposure is expected (studies have not been conducted)
Pregnant women	Use only if potential benefits outweigh the potential risks (no data available)
Breast-feeding women	Consider using only if the expected benefit to the woman is greater than any possible risk to the infant
What other precautions should be taken with its use?	
Patients with acute bronchospasm	Do not use as initial rescue treatment for acute episodes of bronchospasm
Patients in whom paradoxical bronchospasm occurs	Discontinue and consider using other options (paradoxical bronchospasm has not been observed in clinical trials of glycopyrronium bromide, but has been associated with other inhalation therapies)
Patients with a history of cardiovascular disease	Use with caution in patients with unstable ischaemic heart disease, left ventricular failure, history of myocardial infarction, arrhythmia (excluding chronic stable atrial fibrillation), a history of long QT syndrome or prolonged QTcF (experience is limited)
Patients with conditions that may be affected by anticholinergic activity	Use with caution in patients with narrow-angle glaucoma or urinary retention
Are there any potential interactions between glycopyrronium and other drugs?	
Other anticholinergic medications	Coadministration is not recommended (studies have not be conducted)
Other drugs used to treat COPD	No clinical evidence of interaction with inhaled indacaterol (a long-acting β_2-adrenergic receptor agonist)
Inhibitors of organic cation transport	No drug interactions are expected to occur

QTcF QT interval corrected using Fridericia's formula, t_{max} time to peak plasma concentration

Table 2 Efficacy of inhaled glycopyrronium bromide 44 μg once daily in patients with moderate to severe chronic obstructive pulmonary disease in the full-analysis set[a] of the 26-week GLOW1 and 52-week GLOW2 trials

Parameter	Least squares mean between-group difference (glycopyrronium bromide vs. placebo)						
	GLOW 1 [15]			GLOW 2 [13]			
	Day 1	Week 12	Week 26	Day 1	Week 12	Week 26	Week 52
Effect on lung function							
Trough FEV_1 (L)	0.105***	0.108***[b]	0.113***	0.091***	0.097***[b]	0.134***	0.108***
Inspiratory capacity (L)	0.104***	0.097***	0.113***	0.114***	0.129***	0.11***	0.126***
Trough FVC (L)				0.179***	0.183***	0.204***	0.179***
Effect on dyspnoea							
Change from baseline in TDI focal score			1.04***		0.60*	0.81**	0.57*

FEV_1 forced expiratory volume in one second, *FVC* forced vital capacity, *TDI* Transition Dyspnoea Index

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

[a] Included 461–534 and 217–260 patients in the glycopyrronium and placebo arms, respectively, in GLOW1, and 416–513 and 196–250 patients in the glycopyrronium and placebo arms, respectively, in GLOW2

[b] Primary endpoint

bromide than placebo recipients at 26 weeks in GLOW1 [15] and 12, 26 and 52 weeks in GLOW2 [13] (Table 2). In addition, significantly ($p \leq 0.01$) more glycopyrronium bromide than placebo recipients achieved an improvement in TDI focal score that reached the threshold for a minimum clinically important difference (MCID) of ≥1 point in both GLOW1 (61.3 vs. 48.3 %) and GLOW2 (55.3 vs. 44.2 %) at 26 weeks [13, 15].

What is its effect on health status?

In GLOW1 [15], St George's Respiratory Questionnaire (SGRQ) scores were significantly ($p = 0.004$) lower (i.e. better) with inhaled glycopyrronium bromide than with placebo at 26 weeks (LSM 39.50 vs. 42.31 points), but the BGD of −2.81 points did not reach the threshold for a MCID of ≥4 points.

In GLOW2 [13], improvements from baseline in SGRQ scores at weeks 12, 26 and 52 were significantly ($p < 0.001$) better with inhaled glycopyrronium bromide than with placebo (LSM BGD of −3.17, −3.38 and −3.32 points, respectively). Significantly ($p = 0.006$) more glycopyrronium bromide than placebo recipients in GLOW1 achieved an improvement from baseline in SGRQ scores that reached the threshold for a MCID at week 26 (56.8 vs. 46.3 % of patients), but there was no significant BGD at week 52 (54.3 vs. 50.8 %) [13].

What is its effect on COPD exacerbations?

Relative to placebo, inhaled glycopyrronium bromide significantly ($p \leq 0.023$) reduced the risk of having a COPD exacerbation by 31 % in GLOW1 (hazard ratio [HR] 0.69; 95 % CI 0.500, 0.949) [15], and by 34 % in GLOW2 (HR 0.66; 95 % CI 0.520, 0.850) [13], with regard to the time to first COPD exacerbation.

Significant ($p \leq 0.026$) BGD in favour of inhaled glycopyrronium bromide over placebo were observed for other exacerbation-related endpoints, including the risk of hospitalization from severe COPD exacerbation (HR 0.35; 95 % CI 0.141, 0.857) and the proportion of hospitalizations occurring because of COPD exacerbation (odds ratio [OR] 0.34; 95 % CI 0.129, 0.868) in GLOW1 [15], and the annualized rate of moderate or severe COPD exacerbation (rate ratio 0.66; 95 % CI 0.496, 0.869), the number of moderate COPD exacerbations requiring treatment with systemic corticosteroids (OR 0.61; 95 % CI 0.434, 0.870) and the number of moderate COPD exacerbations requiring treatment with antibacterial agents (OR 0.69; 95 % CI 0.495, 0.957) in GLOW2 [13].

What is its effect on rescue medication use?

Inhaled glycopyrronium bromide was also associated with significantly ($p \leq 0.04$) less use of rescue medication than placebo [13, 15]. The BGD in the LSM reduction from baseline in amount of rescue medication used was 0.46 puffs/day at week 26 in GLOW1 [15] and 0.37 puffs/day at week 52 in GLOW2 [13].

What is its effect on exercise tolerance?

The effect of inhaled glycopyrronium bromide on exercise tolerance in 108 patients with moderate to severe COPD was investigated in a 3-week crossover trial (GLOW3) [16]. Glycopyrronium bromide significantly ($p < 0.001$) improved exercise endurance time relative to placebo by ≈10 % on day 1 (LSM 490.9 vs. 447.8 s; BGD 43.1 s) and

≈21 % on day 21 (LSM 505.6 vs. 416.7 s; BGD 88.9 s; primary endpoint) of treatment [16].

Relative to placebo, inhaled glycopyrronium bromide was also associated with significantly ($p < 0.05$) better values for lung hyperinflation during exercise on days 1 and 21, inspiratory capacity just prior to exercise and at peak exercise on days 1 and 21, leg discomfort on exertion on day 21, and exertional dyspnoea on days 1 and 21 [16].

What is its clinical efficacy versus tiotropium bromide in severe to very severe disease?

The randomized, double-blind, 64-week SPARK trial evaluated the efficacy of an inhaled fixed-dose combination of indacaterol and glycopyrronium relative to once-daily monotherapy with inhaled glycopyrronium bromide 50 μg or open-label inhaled tiotropium bromide 18 μg in patients with severe-to-very severe COPD and a history of exacerbation that required treatment with systemic corticosteroids and/or antibacterials during the past year [17]. Preliminary results of a subanalysis of the efficacy of glycopyrronium bromide ($n = 740$) versus tiotropium bromide ($n = 737$) are available as an oral presentation [17].

The efficacy of inhaled glycopyrronium bromide was similar to that of inhaled tiotropium bromide with regard to [17]:

- reductions in the annualized rate of all COPD exacerbations (rate ratio for the BGD 1.01 [95 % CI 0.91, 1.11)
- improvements in lung function (e.g. LSM pre-dose FEV_1 at week 64 was 0.98 vs. 0.99 L; BGD 0.02 L).
- improvements in health status (e.g. 51.8 vs. 50.8 % of patients achieved the MCID of ≥4 units in SGRQ score at 64 weeks)
- reductions in the use of rescue medication (change in the use of rescue salbutamol over the treatment period −1.45 vs. −1.50 puffs per day; BGD 0.05).

What is its tolerability profile?

Inhaled glycopyrronium bromide was generally well tolerated in trials of up to 64 weeks' duration, with most adverse events being mild to moderate in severity and related to the anticholinergic effects of the drug [10, 13, 15, 18].

Data discussed in this section are primarily from a 6-month safety analysis of pooled tolerability data from GLOW1 and the first 6 months of GLOW2 [10]. The most frequently occurring anticholinergic adverse events were dry mouth (2.23 % of inhaled glycopyrronium bromide recipients vs. 1.12 % of placebo recipients), urinary tract infection (1.77 vs. 1.87 %) and constipation (0.93 vs. 1.50 %) [10]. Most cases of dry mouth were reported within the first 4 weeks of treatment and were mild in severity, with none being severe. The median duration for which dry mouth persisted was 4 weeks, although the symptom persisted for the 6-month treatment duration in 40 % of cases. All other anticholinergic adverse events occurred at a low frequency (<1.5 % of patients) in both treatment arms [10].

Study discontinuations because of adverse events occurred in 6.0 % of inhaled glycopyrronium bromide recipients and 8.2 % of placebo recipients during the first 6 months, with respective discontinuation rates at 12 months being 8.0 and 11.6 % [10]. COPD worsening was the most frequently occurring adverse event leading to study discontinuation. COPD worsening was also the most frequently occurring treatment-emergent adverse event overall, occurring in 22.4 % of glycopyrronium bromide recipients and 30.3 % of placebo recipients during the first 6 months [10].

Serious adverse events were consistent with those expected in a population of patients with moderate to severe COPD [10]. In the inhaled glycopyrronium bromide arms, serious adverse events of atrial fibrillation were reported in three patients over the 26-week treatment period in GLOW1 [15] and four patients over the 26-week treatment period of GLOW2 [13]; however, only one of these events in GLOW1 [15] and none of these events in GLOW2 [13] were suspected of being related to treatment.

The overall tolerability profile of inhaled glycopyrronium bromide was similar to that of inhaled tiotropium bromide [10, 18]. The nature of individual treatment-emergent adverse events and serious adverse events, and the percentage of patients discontinuing study drug because of an adverse event in glycopyrronium bromide recipients were similar to those in tiotropium bromide recipients in the pooled analysis of the GLOW trials in patients with moderate to severe COPD [10] and in the SPARK trial in patients with severe to very severe COPD [18]. In the SPARK trial, the overall incidence of adjudicated major adverse cardiovascular events was low, with no clinically meaningful differences between glycopyrronium bromide and tiotropium bromide [18]

Inhaled glycopyrronium bromide was not associated with any clinically relevant changes in laboratory values or vital signs [10, 18].

What is its current positioning?

Inhaled glycopyrronium bromide provides an effective and generally well tolerated option for the long-term

maintenance bronchodilator treatment of adults with moderate to severe COPD in the EU and elsewhere. It has the advantage of once-daily administration, which may potentially improve treatment adherence; other inhaled maintenance LABAs and LAMAs that may be administered once daily include indacaterol, tiotropium bromide and some formulations of formoterol.

Treatment with inhaled glycopyrronium bromide 44 μg once daily is associated with rapid and sustained improvements in lung function, dyspnoea scores, health status, exacerbation rates, use of rescue medication and exercise endurance. It is generally well tolerated, with most adverse events being mild to moderate in severity and related to its anticholinergic effects. The overall efficacy and tolerability profiles of inhaled glycopyrronium bromide are similar to those of inhaled tiotropium bromide. Because of concerns relating to the cardiovascular safety of anticholinergic quaternary ammonium compounds, the post-marketing cardiovascular and cerebrovascular safety of inhaled glycopyrronium bromide is being monitored.

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References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease; 2013. http://www.goldcopd.org. Accessed 18 Sep 2013.
2. Bourbeau J, Bartlett SJ. Patient adherence in COPD. Thorax. 2008;63:831–8.
3. Simoni-Wastila L, Wei Y-J, Qian J, et al. Association of chronic obstructive pulmonary disease maintenance medication adherence with all-cause hospitalization and spending in a Medicare population. Am J Geriatr Pharmacother. 2012;10(3):201–10.
4. Toy EL, Beaulieu NU, McHale JM, et al. Treatment of COPD: relationships between daily dosing frequency, adherence, resource use, and costs. Respir Med. 2011;105:435–41.
5. Cazzola M, Matera MG. Emerging inhaled bronchodilators: an update. Eur Respir J. 2009;34(3):757–69.
6. Agh T, Inotai A, Meszaros A. Factors associated with medication adherence in patients with chronic obstructive pulmonary disease. Respiration. 2011;82:328–34.
7. St Charles M, Blanchette CM, Silver H, et al. Adherence to controller therapy for chronic obstructive pulmonary disease: a review. Curr Med Res Opin. 2010;26(10):2421–9.
8. Seebri® Breezhaler® (glycopyrronium bromide) powder for inhalation: EU summary of product characteristics. London: European Medicines Agency; 2013.
9. Ulrik CS. Once-daily glycopyrronium bromide, a long-acting muscarinic antagonist, for chronic obstructive pulmonary disease: a systematic review of clinical benefit. Int J Chron Obstruct Pulmon Dis. 2012;7:673–8.
10. Seebri® Breezhaler® (glycopyrronium bromide): Committee for Medicinal Products for Human Use assessment report. London: European Medicines Agency; 2012.
11. Sykes DA, Dowling MR, Leighton-Davies J, et al. The influence of receptor kinetics on the onset and duration of action and the therapeutic index of NVA237 and tiotropium. J Pharmacol Exp Ther. 2012;343(2):520–8.
12. Verkindre C, Fukuchi Y, Flémale A, et al. Sustained 24-h efficacy of NVA237, a once-daily long-acting muscarinic antagonist, in COPD patients. Respir Med. 2010;104(10):1482–9.
13. Kerwin E, Hébert J, Gallagher N, et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. Eur Respir J. 2012;40(5):1106–14.
14. Drollmann A, Sechaud R, Pal P, et al. Glycopyrronium does not affect QT interval in healthy subjects: a randomized, 3-period cross-over, placebo- and positive-controlled study [oral presentation no. 4634]. In: European Respiratory Society Annual Congress, 7–11 Sep 2013, Barcelona.
15. 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. Respir Res. 2011;12:156.
16. Beeh KM, Singh D, Di Scala L, et al. Once-daily NVA237 improves exercise tolerance from the first dose in patients with COPD: the GLOW3 trial. Int J Chron Obstruct Pulmon Dis. 2012;7:503–13.
17. Wedzicha JA, Decramer M, Ficker JH, et al. Once-daily glycopyrronium improves lung function and reduces exacerbations in severe-to-very severe COPD patients: the SPARK study [oral presentation no. 180]. In: European Respiratory Society Annual Congress, 7–11 Sep 2013, Barcelona.
18. Decramer M, Wedzicha JA, Ficker JH, et al. Safety of once-daily glycopyrronium in patients with severe-to-very severe COPD: the SPARK study [poster no. P3389]. In: European Respiratory Society Annual Congress, 7–11 Sep 2013, Barcelona.
19. Carter NJ. Inhaled glycopyrronium bromide: a review of its use in patients with moderate to severe chronic obstructive pulmonary disease. Drugs. 2013;73(7):741–53.