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ADIS DRUG EVALUATION

Inhaled Glycopyrronium Bromide: A Review of its Use in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease

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Abstract Inhaled glycopyrronium bromide (Seebri® Breezhaler® capsules; NVA237) is a once-daily, long-acting muscarinic receptor antagonist (LAMA) that is approved in several countries, including the EU, as a maintenance bronchodilator for the symptomatic treatment of adult patients with chronic obstructive pulmonary disease (COPD). In the randomized, controlled, phase III GLOW (GLycopyrronium bromide in chronic Obstructive pulmonary disease airWays clinical study)-1 and -2 trials, treatment with inhaled glycopyrronium bromide 50 μg once daily was associated with significantly better lung function than placebo in patients with moderate to severe COPD in terms of the trough forced expiratory volume in one second (FEV_1) at 12 weeks (primary endpoint). Significant between-group differences in trough FEV_1 in favour of inhaled glycopyrronium bromide were maintained for up to 52 weeks. Dyspnoea scores, health status and exacerbation rates were also improved to a greater extent in the inhaled glycopyrronium bromide than placebo groups in these trials. In the randomized, controlled, phase III GLOW3 trial, inhaled glycopyrronium bromide was associated with a significantly longer exercise endurance time than placebo after 3 weeks' treatment in patients with moderate to severe COPD. The drug was generally well tolerated over the 26-week (GLOW1) or 52-week (GLOW2) study duration, and had a tolerability profile that was generally similar to that of tiotropium bromide. Serious adverse events were consistent with those expected in patients with moderate to severe COPD. In conclusion, inhaled glycopyrronium bromide is a once-daily LAMA that is an effective bronchodilator for use in the treatment of patients with moderate to severe COPD.

Inhaled glycopyrronium bromide in patients with moderate to severe chronic obstructive pulmonary disease (COPD): a summary

A once-daily, long-acting muscarinic receptor antagonist that bronchodilates the airways by inhibiting acetylcholine-induced bronchoconstriction in bronchial smooth muscle cells

Significantly improves lung function compared with placebo in patients with moderate to severe COPD

Associated with better exercise endurance than placebo in patients with moderate to severe COPD

Is generally well tolerated, with dry mouth being the most frequent potentially treatment-related adverse event

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1 Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease that is caused by inflammation in the lung and airways that leads to a variable combination of parenchymal tissue destruction (emphysema) and small

airways disease (obstructive bronchiolitis) and, ultimately, limited airflow [1]. The most common symptoms of COPD are respiratory in nature (e.g. dyspnoea, cough and increased sputum production), but extrapulmonary symptoms (e.g. weight loss, anaemia and skeletal muscle atrophy) and comorbidities (e.g. cardiovascular disease, lung cancer and osteoporosis) are also common [1, 2]. Cigarette smoking is the most common risk factor for COPD and, as such, the disease is largely preventable [1–3].

Although pharmacological treatments are available, COPD is generally progressive and is a major cause of morbidity and mortality worldwide [1]. The prevalence of COPD in Europe is estimated to be between 2.1 and 26.1 %, depending on country-specific factors, age group and the methods used to obtain the data [3]. The World Health Organization predicts that, by 2030, COPD will become the third most common cause of death globally [4]. COPD is also associated with a large economic and social burden and, thus, is a major public health concern [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 other quality-of-life measures [1]. Drugs that bronchodilate the airways (bronchodilators) play a key role in the management of COPD symptoms, with preference generally given to long-acting versus short-acting agents and inhaled versus orally administered agents, such as the inhaled long-acting muscarinic receptor antagonists (LAMAs; e.g. glycopyrronium bromide [5], aclidinium bromide [6] and tiotropium bromide) and long-acting β_2-adrenergic receptor agonists (LABAs; e.g. formoterol, indacaterol and salmeterol) [1].

As is the case for many other chronic diseases [7], patient adherence to COPD therapy is often suboptimal [7–11], and this in turn may be associated with poor clinical outcomes and increased healthcare costs [7, 12]. Many factors influence adherence to COPD therapy [7, 9, 11], including patient characteristics (e.g. age), prior treatment, disease severity, convenience of the treatment regimen and patient education [9]. Dosage frequency has also been shown to be associated with adherence to COPD treatment [7–9, 13, 14], and it has been suggested that this may be improved by minimizing the dosage frequency of the agent [7–9]. Many LAMAs (e.g. aclidinium bromide) and LABAs (e.g. salmeterol, formoterol) are dosed twice daily and, thus, finding agents that can be dosed once daily is likely to be an important step in the attempt to improve patient adherence [15].

Inhaled glycopyrronium bromide (Seebri® Breezhaler® capsules; NVA237) is approved in various countries, including the EU (Sect. 6), as a maintenance bronchodilator for the symptomatic treatment of adult patients with COPD, and is one of few bronchodilators available in the EU to be administered once daily [5]. Others are indacaterol (a LABA) [16] and tiotropium bromide (a LAMA) [17, 18]; some formulations of formoterol (a LABA) may also be administered once or twice daily [19, 20]. This article reviews the pharmacology, therapeutic efficacy and tolerability of inhaled glycopyrronium bromide in patients with moderate to severe COPD.

Each Seebri® Breezhaler® capsule contains 63 μg of glycopyrronium bromide, which is equivalent to 50 μg of glycopyrronium, and each delivered dose (i.e. the amount of drug that leaves the inhaler) contains 55 μg of glycopyrronium bromide, which is equivalent to 44 μg of glycopyrronium [5]. Dosages of inhaled glycopyrronium bromide in this article are for the equivalent administered (not delivered) dose of glycopyrronium.

Data selection

Sources: Medical literature (including published and unpublished data) on 'inhaled glycopyrronium bromide in patients with moderate to severe chronic obstructive pulmonary disease' was identified by searching databases, including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 25 March 2013], bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug.

Search terms: 'glycopyrronium bromide', 'chronic obstructive pulmonary disease'.

Study selection: Studies in patients with chronic obstructive pulmonary disease who received inhaled glycopyrronium bromide. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Keywords: Glycopyrronium, glycopyrronium bromide, glycopyrrolate, NVA237, chronic obstructive pulmonary disease, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

2 Pharmacodynamic Properties

2.1 Mechanism of Action

The pharmacodynamic properties of glycopyrronium bromide have been investigated in in vitro [21], ex vivo [21–

23] and animal [23, 24] studies. Further data pertaining to the in vitro pharmacodynamics of glycopyrronium bromide were obtained from the manufacturer's prescribing information [5] and the European Medicines Agency (EMA) assessment report for inhaled glycopyrronium bromide [25]. The receptor kinetics of both glycopyrronium bromide and tiotropium bromide were altered by in vitro testing under physiological (11.4 and 46.2 min for the M_3 muscarinic receptor) versus nonphysiological (173 and 462 min) conditions in terms of the dissociation half-lives of the two drugs [21]. Thus, apart from onset of action data from an in vitro calcium assay, in vitro data from this study discussed here are those obtained from testing at a physiological temperature of 37 °C and in a physiologically relevant buffer containing sodium chloride 138 nmol/L [21].

Glycopyrronium bromide, a quaternary ammonium compound, is a competitive muscarinic receptor antagonist that bronchodilates the airways by inhibiting acetylcholine-induced bronchoconstriction in bronchial smooth muscle cells [5, 25, 26].

Of the three muscarinic receptor subtypes thought to be relevant to the human lung (i.e. the M_1–M_3 receptors) [25], it is the M_3 receptor that is thought to be the prime mediator of cholinergic bronchoconstriction [25, 26]. In contrast, the M_2 receptor protects against bronchoconstriction [25, 26], and has a role in cardiac function (e.g. blocking of the M_2 receptor may increase heart rate) [26, 27]. Hence, ideal bronchodilator agents have high affinity for the M_3 (and M_1) receptor, but low affinity for the M_2 receptor [25, 26]. In vitro, glycopyrronium bromide binds with high affinity to the M_1, M_2 and M_3 receptors, and has 4- to 5-fold higher selectivity for human M_1 and M_3 receptors than for the human M_2 receptor (equilibrium binding affinity constants of 9.60–9.81 and 9.47–9.64 vs. 8.70–9.25 [25]) [21, 25]. In addition, glycopyrronium bromide dissociates slower from the M_3 and M_1 receptors than from the M_2 receptor (dissociation half-life 11.4 and 13.9 vs. 1.07 min; kinetic off rate 0.061 and 0.05 vs. 0.646 per min [21]) [21, 25].

Glycopyrronium bromide had a 2.5- to 4.8-fold faster onset of action than tiotropium bromide in terms of the time taken to achieve 50 % inhibition of methacholine-stimulated calcium release in hamster ovarian cells stably expressing M_3 receptors (6.1 vs. 29.4 min) or bethanechol-stimulated contraction in rat tracheal strips (9.8 vs. 24.6 min) [21]. Equilibrium binding affinity constants further indicate that glycopyrronium bromide has a faster onset of action at the M_3 receptor in vitro than tiotropium bromide (9.59 vs. 10.37) [21]. Moreover, the $\approx$4-fold faster kinetic off rate (0.061 vs. 0.015 per min) seen in vitro suggests that glycopyrronium bromide will reach equilibrium faster than tiotropium bromide [21].

The faster onset of action of glycopyrronium bromide versus tiotropium bromide was supported by results of a phase II study, in which patients ($n = 83$) with moderate to severe COPD received inhaled glycopyrronium bromide 12.5–100 μg, tiotropium bromide 18 μg or placebo once daily for 7 days [28]. The difference in forced expiratory volume in one second (FEV_1) values between the inhaled glycopyrronium bromide 50-μg or 100-μg and tiotropium 18-μg arms was significantly ($p < 0.05$) in favour of inhaled glycopyrronium bromide from 5 min to 2 h (50-μg dosage) or 4 h (100-μg dosage) post-dose on day 1. However, this was not apparent on day 7. Further details regarding the effects of inhaled glycopyrronium bromide on lung function in adult patients with COPD participating in clinical trials are discussed in Sect. 4.

Glycopyrronium bromide showed greater equilibrium binding selectivity (M_3 selectivity ratio [ratio of the affinity constant for the M_3 receptor vs. that for the M_2 receptor] of 7.76-fold vs. 2.09-fold) and kinetic selectivity (M_3 kinetic selectivity ratio [ratio of the area under the simulated association and dissociation curves for the M_3 receptor vs. that for the M_2 receptor] of 11.41-fold vs. 4.30-fold) for M_3 versus M_2 than tiotropium bromide, indicating the potential for an improved therapeutic index [21].

Glycopyrronium bromide concentration-dependently inhibited electrical field stimulation (EFS)-induced [22] and carbachol-induced [23] contraction of human isolated airways at nanomolar concentrations. Furthermore, glycopyrronium bromide was more potent than ipratropium bromide and/or tiotropium bromide in terms of the concentration [22] or −log molar concentration [23] required to inhibit the contractile response by 50 % (Table 1).

The onset of action of glycopyrronium bromide was similar to that of ipratropium bromide in terms of the time taken to attain 50 % inhibition of the EFS-induced contractile response in human isolated airways (Table 1) [22]. However, glycopyrronium bromide inhibited the contractile response for a numerically longer duration than ipratropium bromide with regard to the time taken from investigational drug washout to attain 50 % recovery of the EFS-induced [22] or carbachol-induced [23] contractile response ($t_{½}$ offset) [Table 1]. In contrast, glycopyrronium bromide and ipratropium bromide were both more rapidly reversible than tiotropium bromide in terms of $t_{½}$ offset values and the percentage recovery of the carbachol-induced contractile response attained 6 h after investigational drug washout (Table 1) [23].

In studies of anaesthetized animals, acetylcholine-induced bronchospasm was dose-dependently inhibited by intra-tracheal administration of all LAMAs under investigation, including inhaled glycopyrronium bromide, with peak inhibitory effects generally exceeding 80 % at the highest administered dose (Table 1) [23, 24].

Table 1 Comparative pharmacology of glycopyrronium bromide and other LAMAs

Parameter	GLY	ACL	IPR	TIO
Effect on human isolated airways[a]				
Haddad et al. [22]				
IC_{50} (nmol/L)	0.44		1.36	
$t_{½}$ onset (min)[b]	19.7		14.9	
$t_{½}$ offset (min)[b]	<96		59.1	
Villetti et al. [23]				
pIC_{50}	10.4		9.5	9.5
$t_{½}$ offset (h)[b]	3.7		3.0	>6.0
Recovery at 6 h[b,c] (%)	101		110	27
Effect in anaesthetized animals				
Casarosa et al. [24]				
Bronchoprotection[d,e] (%) at:				
Peak[f]	85	73		86
3 h	49	52		73
24 h	0	21		35
Villetti et al. [23]				
Bronchoprotection[d,g] (%) at:				
Peak	88.1		88.1	86.2
3 h	69.9		28.3	83.5
24 h	29.7		14.2	70.6

ACL aclidinium bromide, *EFS* electrical field stimulation, *GLY* glycopyrronium bromide, IC_{50} concentration of investigational drug required to inhibit contractile response by 50 %, *IPR* ipratropium bromide, *LAMAs* long-acting muscarinic receptor antagonists, pIC_{50} −log molar concentration of investigational drug required to inhibit contractile response by 50 %, *TIO* tiotropium bromide, $t_{½}$ *offset* time taken from washout of investigational drug to attain 50 % recovery of contractile response, $t_{½}$ *onset* time taken from administration of investigational drug to attain 50 % inhibition of contractile response

[a] Effect on EFS-induced contraction in tracheal strips and bronchial rings from the lungs of patients receiving heart or heart and lung transplantation [22], and on carbachol-induced contraction in bronchial rings from the lungs of patients undergoing surgery for lung cancer [23]

[b] Drugs were administered at the following concentrations: GLY 3 nmol/L, IPR 10 nmol/L and TIO 1 nmol/L

[c] Percentage recovery of contractile response attained 6 h after investigational drug washout

[d] Peak inhibitory effect on acetylcholine-induced bronchospasm and inhibitory effect at 3 h and 24 h after study drug administration

[e] Data were obtained after administration of each drug at a fully effective dose (i.e. at the dose known to induce 80 % bronchoprotection) of GLY 12 µg/animal, ACL 30.0 µg/animal or TIO 3 µg/animal

[f] Values were estimated from a graph

[g] Data were obtained after administration of each drug at the highest tested dose of GLY 3 nmol/kg, IPR 1.45 nmol/kg or TIO 1.3 nmol/kg

Glycopyrronium bromide-associated bronchoprotection (see Table 1 for definition) at 3 and 24 h after study drug administration was intermediate between that for ipratropium bromide [23] and that for tiotropium bromide [23, 24] (Table 1). Bronchoprotection was similar for glycopyrronium bromide and aclidinium bromide at 3 h after study drug administration, but numerically lower for glycopyrronium bromide than for aclidinium bromide at 24 h (Table 1) [24].

2.2 Effects on the QT Interval

Inhaled glycopyrronium bromide had no relevant effect on the QTc interval (corrected using Fridericia's formula [QTcF]) when administered at a supratherapeutic single dose of 400 µg, according to data from a positive-controlled QTc study reported in the EMA assessment document [25]. The mean effect on QTcF was below the prespecified threshold of 5 ms, and the upper limit of the 95 % confidence interval for the mean effect was below the prespecified threshold of 10 ms.

3 Pharmacokinetic Properties

3.1 Absorption and Distribution

Glycopyrronium bromide is rapidly absorbed into the systemic circulation after inhalation, ≈90 % via lung absorption and ≈10 % via gastrointestinal absorption [5]. On days 1 and 14 in a double-blind, multicentre study in patients ($n = 41$) with mild to moderate COPD, the maximum glycopyrronium bromide plasma concentration (C_{max}) was achieved a median of 5 min after study drug administration in those patients ($n = 8$) who received inhaled glycopyrronium bromide at the recommended dosage of 50 µg once daily [29] (Sect. 6). The absolute systemic bioavailability of glycopyrronium bromide after inhalation is estimated to be ≈45 % of the delivered dose [25]. Plasma concentrations of glycopyrronium bromide reached steady state within 1 week of receiving inhaled glycopyrronium bromide 25–200 µg once daily in the COPD study [5, 29].

On day 14 in the COPD study, inhaled glycopyrronium bromide systemic exposure (i.e. C_{max} and area under the plasma concentration-time curve [AUC] over a 24-h dosing period [AUC_{24}]) was approximately dose-proportional over the dosage range of 50–200 µg once daily [29]. In patients who received inhaled glycopyrronium bromide 50 µg once daily, the mean glycopyrronium bromide C_{max} was 166 pg/mL and the mean AUC_{24} was 464 pg · h/mL on day 14 [29]. Mean glycopyrronium bromide AUC_{24} was 1.4- and 1.7-fold higher on day 14 than on day 1 in patients receiving inhaled glycopyrronium bromide 100 or 200 µg once daily [29].

The volume of distribution (V_d) of glycopyrronium bromide at steady state was 83 L after intravenous

administration, and the V_d in the terminal phase was 376 L [5, 25]. After inhalation of glycopyrronium bromide, the V_d in the terminal phase was 7,310 L, with the large ($\approx$20-fold) difference reflecting the slower glycopyrronium bromide elimination seen after inhalation than after intravenous administration (see Sect. 3.2) [25]. At concentrations of 1–10 ng/mL, $\approx$38–41 % of glycopyrronium bromide was bound to human plasma proteins in vitro [5, 25].

3.2 Metabolism and Elimination

Glycopyrronium bromide is hydrolyzed to form the major circulating metabolite, M9, which is a carboxylic acid derivative [5]; M9 was inactive against all tested targets in vitro [25]. The metabolite is thought to be formed from the swallowed fraction of inhaled glycopyrronium bromide [5, 25], and has a plasma concentration that is approximately the same as that of the parent drug after inhalation but not after intravenous administration [25].

Glycopyrronium bromide also formed various mono- and bis-hydroxylated metabolites in vitro, and glucuronide and sulfate conjugates of glycopyrronium bromide were seen in the urine of subjects receiving multiple dosages of inhaled glycopyrronium bromide [5]. Several cytochrome P450 (CYP) enzymes are thought to contribute to the oxidative biotransformation of glycopyrronium bromide [5, 25], with CYP2D6 being the most quantitatively important [25].

Systemically available glycopyrronium bromide is predominantly (60–70 %) cleared from the plasma via renal elimination of the parent drug [5, 25]. Other elimination routes account for 30–40 % of the total plasma clearance of the drug, mainly metabolism and, to a lesser extent (up to 5 % [25]), biliary clearance [5, 25].

In patients with COPD, the mean renal clearance of inhaled glycopyrronium bromide 50 μg once daily was 17.6 L/h on day 14 [29]. Up to 23 % of the delivered dose of inhaled glycopyrronium bromide is excreted in the urine as unchanged drug, and about 3 % of the total dose is excreted in the urine as glucuronide and/or sulfate conjugates [5]. The urinary excretion of unchanged drug increased approximately dose-proportionally over the dosage range of 50–200 μg once daily in patients with COPD [29].

In the 48 h after intravenous administration of ^{3}H-labelled glycopyrronium bromide, the mean urinary excretion of radioactivity was 85 % of the administered dose and a further 5 % was found in the bile [5].

Glycopyrronium bromide has a multiphasic elimination profile, with a mean terminal elimination half-life in healthy volunteers that is longer after inhalation of the drug than after intravenous or oral administration (33–57 vs. 6.2 and 2.8 h) [5]. In the COPD study, the mean glycopyrronium bromide terminal elimination half-life was 13.4 h after 14 days' treatment with inhaled glycopyrronium bromide 50 μg once daily [29]. After inhalation of glycopyrronium bromide, the elimination profile of glycopyrronium bromide indicates that there is sustained absorption (e.g. via lung absorption or other transfer methods) of the drug into the systemic circulation for $\geq$24 h after administration [5].

3.3 Special Populations

Data from a population pharmacokinetic analysis demonstrated that patient age and bodyweight contributed to the interpatient variability in inhaled glycopyrronium bromide systemic exposure in patients with COPD [5]. However, no adjustments to the dosage of inhaled glycopyrronium bromide are thought necessary on the basis of these results [5]. The pharmacokinetics of inhaled glycopyrronium bromide were not altered to a clinically relevant extent by race (Caucasian vs. Japanese), gender, smoking status or baseline FEV_1 value [5].

Studies of inhaled glycopyrronium bromide have not been conducted in patients with hepatic impairment. However, because glycopyrronium bromide is predominantly cleared from the plasma via renal elimination (Sect. 3.2), systemic exposure of the drug is not expected to be increased to a clinically relevant extent in patients with hepatic impairment, and no adjustments in the dosage of inhaled glycopyrronium bromide are thought necessary in such patients [5].

Inhaled glycopyrronium bromide AUC from time zero until the last measurable concentration (AUC_{last}) was up to 1.4-fold higher in patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] $\geq$30 mL/min/1.73 m^2) than in those with normal renal function, and up to 2.2-fold higher in those with severe renal impairment (eGFR $<$30 mL/min/1.73 m^2) or end-stage renal disease [5]. Patients with mild or moderate renal impairment may receive inhaled glycopyrronium bromide at the recommended dosage of 50 μg once daily, but the drug should only be used in patients with severe renal impairment or end-stage renal disease requiring dialysis if the benefits of treatment outweigh the potential risks [5].

3.4 Drug Interactions

Glycopyrronium bromide does not inhibit or induce drug transporters (e.g. the efflux transporters multidrug resistant protein-1 and multidrug resistance-associated protein-2) or any enzymes involved in drug metabolism (e.g. CYP isozymes) to a clinically meaningful degree and, thus, the potential for drug interactions is low [25].

Table 2 Key design details and baseline patient characteristics in the phase III, randomized, double-blind, multicentre, parallel-group [30, 31] or crossover [32] GLOW trials

	GLOW1 [30][a]		GLOW2 [31][a]			GLOW3 [32][b]	
	GLY ($n = 550$)	PL ($n = 267$)	GLY ($n = 525$)	TIO ($n = 267$)	PL ($n = 268$)	GLY ($n = 55$)	PL ($n = 53$)
Selected pt characteristics at baseline by treatment group (no. of pts in safety population)							
Current smoker (% of pts)	32.7	34.1	45.3	44.2	46.3	51	70
Mean smoking duration (pack-years)	44.9	44.6	49.0	50.2	48.0	41.4	51.0
Mean FEV_1[c] (L)	1.49	1.45	1.5	1.5	1.5	1.6	1.7
Mean FEV_1[c] (% predicted)	54.75	54.33	55.7	56.0	56.4	57.3	57.0
Mean FEV_1:FVC ratio[c] (%)	50.15	49.92	50.6	50.3	50.9	50	50
Key inclusion criteria							
In all studies: male or female; aged ≥40 years; COPD meeting the GOLD definition of moderate to severe disease; smoking history of ≥10 pack-years; baseline FEV_1 of ≥30 % (or ≥40 % [32]) and <80 % of predicted normal[c]; FEV_1:FVC ratio of <70 %[c]							
In GLOW2: stable COPD							
Key exclusion criteria							
In all studies: history of LRTI within the previous 6 weeks; other concomitant pulmonary disease; history of asthma, lung cancer, long QT syndrome (or a corrected QT interval of >450 ms [male] or >470 ms [female]), symptomatic prostatic hyperplasia, bladder neck obstruction, moderate or severe renal impairment, urinary retention, narrow-angle glaucoma or α_1-antitrypsin deficiency; any supervised participation in a pulmonary rehabilitation programme; presence of any contraindication or previous adverse reactions to TIO, IPR or other inhaled anticholinergic agents [30–32]							
In GLOW2 and/or GLOW3: history of malignancy (excluding localized basal cell carcinoma) [31, 32], chronic hypoxaemia requiring oxygen [31, 32], hospitalization for COPD exacerbation within previous 6 weeks [31] and/or previous adverse reactions to long- or short-acting β_2-adrenergic-receptor agonists or sympathomimetic amines [32]							
Primary efficacy endpoint							
In GLOW1 and GLOW2: trough FEV_1[d] after 12 weeks' treatment							
In GLOW3: exercise endurance time during a SMET after 3 weeks' treatment							

COPD chronic obstructive pulmonary disease, *FEV_1* forced expiratory volume in one second, *FVC* forced vital capacity, *GLY* glycopyrronium bromide, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *IPR* ipratropium bromide, *LRTI* lower respiratory tract infection, *PL* placebo, *pt(s)* patient(s), *SDDPI* single-dose dry-powder inhaler, *SMET* Submaximal Constant-Load Cycle Ergometry Test, *TIO* tiotropium bromide

[a] Following prescreening [30] or washout [31] periods of ≤7 days and a run-in period of 14 days [30, 31], pts received double-blind GLY 50 μg or PL inhaled once daily via a low resistance SDDPI for 26 [30] or 52 [31] weeks. In GLOW2, pts received open-label TIO 18 μg inhaled once daily via the Handihaler® device for 52 weeks [31]

[b] Pts received double-blind GLY 50 μg inhaled once daily for 3 weeks followed (after a 14–21 day washout period) by PL inhaled once daily for 3 weeks or vice versa. Both study treatments were administered via a low resistance SDDPI

[c] Postbronchodilator assessments

[d] Defined as the mean of the FEV_1 values performed at 23 h 15 min and 23 h 45 min after the last dose of study drug

Glycopyrronium bromide is a substrate for the transporters organic cation transporter (OCT)-2 and multidrug and toxin extrusion protein (MATE)-1, and coadministration of inhaled glycopyrronium bromide with (as opposed to without) cimetidine (an OCT2 and MATE1 inhibitor) resulted in a 22 % increase in glycopyrronium bromide AUC_{last} and a 23 % decrease in renal clearance [25]. However, these changes were not considered to be clinically relevant and, thus, inhaled glycopyrronium bromide may be coadministered with cimetidine or other organic cation transport inhibitors [5].

No studies are available regarding the concomitant administration of inhaled glycopyrronium bromide and other anticholinergic agents [5]. Thus, the combination is not recommended.

Coadministration of inhaled glycopyrronium bromide and indacaterol (a LABA) did not affect the pharmacokinetics of either drug at steady state [5].

4 Therapeutic Efficacy

The efficacy of inhaled glycopyrronium bromide in patients with moderate to severe COPD was assessed in two phase III trials known as the GLOW (GLycopyrronium bromide in chronic Obstructive pulmonary disease airWays clinical study)-1 [30] and -2 [31] trials. A third phase III trial, the GLOW3 trial, investigated the effect of inhaled glycopyrronium bromide on exercise tolerance in patients with

moderate to severe COPD [32]. Because GLOW3 was a smaller ($n = 108$ [32] vs. 822 [30] and 1,066 [31]) study and of shorter duration (3 weeks vs. 26 and 52 weeks) than GLOW1 and GLOW2, only data pertaining to the effect of inhaled glycopyrronium bromide on exercise tolerance and exercise-related symptomatology from GLOW3 are discussed (Sect. 4.6). Mean patient age was ≈64 years in GLOW1 [30] and GLOW2 [31], and ≈60 years in GLOW3 [32]. In GLOW1 [30] and GLOW2 [31], the proportion of patients with COPD meeting Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for moderate, severe or very severe disease was 60–65, 34–40 and 0–1.1 %, respectively, across all treatment groups; these data were not reported for GLOW3 [32]. Key design details of the GLOW trials and other patient baseline characteristics are shown in Table 2. Although open-label inhaled tiotropium bromide was included as a reference comparator in GLOW2, the study was not powered to show statistical superiority of inhaled glycopyrronium bromide over inhaled tiotropium bromide [31].

Table 3 Efficacy of inhaled glycopyrronium bromide in patients with moderate to severe chronic obstructive pulmonary disease. Results of the 26-week GLOW1 and 52-week GLOW2 trials (see also Table 2). Analyses were conducted in the full analysis set[a]

Endpoint (LSM treatment difference[b])	GLOW1 [30]	GLOW2 [31]		
	GLY vs. PL	GLY vs. PL	TIO vs. PL	GLY vs. TIO
Effect on Lung Function (*Spirometery-Assessed Parameters*)				
Trough FEV_1[c] (L) at end of:				
Day 1	0.105***	0.091***	0.083***	0.008
Week 12[d]	0.108***	0.097***	0.083***	0.014
Week 26	0.113***	0.134***	0.084***	0.050††
Week 52		0.108***	0.089***	0.019
Inspiratory capacity (L) at end of[e]:				
Day 1	0.104***	0.114***	0.080**	0.033
Week 12	0.097***	0.129***	0.113**	0.015
Week 26	0.113***	0.11***	0.081*	0.029
Week 52		0.126***	0.084*	0.042
Trough FVC[c] (L) at end of:				
Day 1		0.179***	0.172***	0.006
Week 12		0.183***	0.168***	0.015
Week 26		0.204***	0.134***	0.070†
Week 52		0.179***	0.180***	−0.001
Effect on Dyspnoea				
Change from BL in TDI focal score at:				
Week 12		0.60*	0.26	0.34
Week 26	1.04***	0.81**	0.94**	−0.13
Week 52		0.57*	0.66*	−0.08
Effect on Health Status				
Change from BL in SGRQ score at:				
Week 12		−3.17***	−2.84**	−0.33
Week 26	−2.81**[f]	−3.38***	−2.52*	−0.86
Week 52		−3.32***	−2.84*	−0.48

BL baseline, *FEV_1* forced expiratory volume in one second, *FVC* forced vital capacity, *GLY* glycopyrronium bromide, *LSM* least squares mean, *PL* placebo, *SGRQ* St George's Respiratory Questionnaire, *TDI* Transition Dyspnoea Index, *TIO* tiotropium bromide

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. PL; † $p < 0.05$, †† $p < 0.01$ vs. TIO

[a] The number of patients included in these efficacy analyses in GLOW1 was 461–534 in the GLY arm and 217–260 in the PL arm and, in GLOW2, 416–513 in the GLY arm, 210–253 in the TIO arm and 196–250 in the PL arm

[b] Unless otherwise specified, data given here are the LSM difference in LSM values for each parameter

[c] Defined as the mean of the FEV_1 or FVC values performed at 23 h 15 min and 23 h 45 min after the last dose of study drug

[d] Primary endpoint

[e] At 23 h 40 min after the last dose of study drug

[f] LSM treatment difference in actual SGRQ score at week 26 (not the change from BL in SGRQ score)

Data from these pivotal phase III trials are supported by those of randomized, double-blind, placebo-controlled, multicentre phase II studies ($n = 33$–385) in patients with mild to severe [33] or moderate to severe [28, 34, 35] COPD. Based on results from one of these studies [28], the EMA did not consider that inhaled glycopyrronium bromide 100 μg once daily offered any significant advantage in efficacy over the 50-μg once-daily dosage [25], with this latter dosage being used in the pivotal phase III trials [30–32].

The effectiveness of inhaled glycopyrronium bromide 50 μg once daily was also supported by results of a 28-day dose-finding trial that used a novel model-based approach to evaluate the efficacy of once-daily and twice-daily dosage regimens [34]. Based on results from this study, the EMA concluded that inhaled glycopyrronium bromide 50 μg or 100 μg once daily had comparable effects on trough FEV_1 and that the 50-μg once-daily regimen had "clearly demonstrated efficacy" [25]. However, because some data were available to suggest that inhaled glycopyrronium bromide 25 μg twice daily may potentially be better than the 50-μg once-daily regimen in terms of efficacy and safety, the EMA requested a post-authorization study to further evaluate the optimal dosing schedule of the drug [25].

4.1 Effect on Lung Function

In GLOW1 [30] and GLOW2 [31], treatment with inhaled glycopyrronium bromide 50 μg once daily was associated with better lung function than placebo in patients with moderate to severe COPD in terms of the trough FEV_1 assessed at 12 weeks (primary endpoint) [Table 3]. Significant between-group differences in trough FEV_1 in favour of inhaled glycopyrronium bromide were also observed at the first assessment at the end of day 1 [30, 31], and after 26 weeks [30, 31] and 52 weeks [31] of treatment (Table 3). 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 inhaled glycopyrronium bromide than in recipients of placebo in GLOW2 [31].

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 inhaled glycopyrronium bromide than placebo recipients in both GLOW1 [30] and GLOW2 [31].

Inhaled glycopyrronium bromide was associated with a significantly ($p < 0.05$) higher inspiratory capacity than placebo at all assessed time points on day 1 [30, 31] and at weeks 12 [30, 31], 26 [30, 31] and 52 [31] (see also Table 3).

Trough forced vital capacity (FVC) was also significantly higher in inhaled glycopyrronium bromide than placebo recipients at the end of day 1 and after 12, 26 and 52 weeks of treatment in GLOW2 (Table 3) [31].

Inhaled tiotropium bromide 18 μg once daily was also associated with significantly better lung function than placebo in GLOW2 (Table 3) [31]. In general, there were no significant differences between inhaled glycopyrronium bromide and tiotropium bromide in values for key spirometry-assessed parameters (Table 3). However, trough FEV_1 and trough FVC were both significantly higher in inhaled glycopyrronium bromide than tiotropium bromide recipients after 26 weeks' treatment, but not after 12 or 52 weeks' treatment (Table 3). In addition, inhaled glycopyrronium bromide appeared to have a faster onset of action than tiotropium bromide on day 1, with FEV_1 values obtained at 5 min and at 15 min after administration of the study drug being significantly ($p < 0.01$) higher in inhaled glycopyrronium bromide than tiotropium bromide recipients [31].

4.2 Effect on Dyspnoea

Inhaled glycopyrronium bromide improved symptoms of dyspnoea to a greater extent than placebo, with the change (increase) in Transition Dyspnoea Index (TDI) focal score from baseline to the end of week 26 being significantly greater in inhaled glycopyrronium bromide than placebo recipients in both GLOW1 [30] and GLOW2 [31] (Table 3). In addition, this between-group difference exceeded the threshold for a minimum clinically important difference (MCID) of ≥1 point in GLOW1 [30]. Significantly ($p \leq 0.01$) more patients receiving inhaled glycopyrronium bromide than those receiving placebo achieved an improvement in TDI focal score from baseline to week 26 that reached the threshold for a MCID in both GLOW1 (61.3 vs. 48.3 %) [30] and GLOW2 (55.3 vs. 44.2 %) [31]. The change in TDI focal score from baseline to the end of weeks 12 or 52 was also significantly greater in inhaled glycopyrronium bromide recipients than placebo recipients in GLOW2 (Table 3) [31].

In GLOW2, tiotropium bromide improved the TDI focal score from baseline to weeks 26 and 52 (but not from baseline to week 12) to a significantly greater extent than placebo (Table 3). A total of 53.4 % of tiotropium bromide recipients achieved a MCID in this parameter ($p = 0.032$ vs. placebo) [31]. No significant differences were seen between the two active treatment arms in terms of the change in TDI focal scores from baseline to week 12, 26 or 52 (Table 3) [31].

4.3 Effect on Health Status

Inhaled glycopyrronium bromide was associated with a significantly lower St George's Respiratory Questionnaire

(SGRQ) score than placebo after 26 weeks' treatment in GLOW1, but this between-group difference did not reach the threshold for a MCID of ≥4 points (Table 3) [30]. In GLOW2, the change (decrease) in SGRQ scores from baseline to weeks 12, 26 and 52 was significantly greater in inhaled glycopyrronium bromide than placebo recipients (Table 3) [31]. Significantly ($p = 0.006$) more inhaled glycopyrronium bromide than placebo recipients in GLOW1 achieved an improvement from baseline to week 26 in SGRQ scores that reached the threshold for a MCID (56.8 vs. 46.3 % of patients) [30]. In GLOW2, the proportion of patients achieving an improvement from baseline to week 52 in SGRQ scores that reached the threshold for a MCID was 54.3 % in the inhaled glycopyrronium bromide group and 50.8 % in the placebo group [31].

Significantly greater improvements in SGRQ scores from baseline to weeks 12, 26 and 52 were also seen between the tiotropium bromide versus placebo arms, but not between the inhaled glycopyrronium bromide versus tiotropium bromide arms (Table 3) [31]. A total of 59.4 % of tiotropium bromide recipients achieved an improvement from baseline to week 52 in SGRQ scores that reached the threshold for a MCID.

4.4 Effect on COPD Exacerbations

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) [30] and by 34 % in GLOW2 (HR 0.66; 95 % CI 0.520–0.850) [31] compared with placebo with regard to the time to first COPD exacerbation.

Significant ($p \leq 0.026$ vs. placebo) between-group differences in favour of inhaled glycopyrronium bromide were observed for other exacerbation-related endpoints assessed in GLOW1 [30] and GLOW2 [31]. These included 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 [30], 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 [31]. However, no statistically significant difference was seen between inhaled glycopyrronium bromide and placebo recipients in the proportion of patients with one or more moderate or severe COPD exacerbation(s) or in the annualized rate of moderate or severe COPD exacerbations in GLOW1 [30].

In GLOW2, the risk of having a COPD exacerbation was reduced by 39 % in the tiotropium bromide versus placebo arms ($p = 0.001$; HR 0.61; 95 % CI 0.456–0.821) [31]. Apart from the difference between tiotropium bromide and placebo in the rate of moderate or severe COPD exacerbation, which was not statistically significant, tiotropium bromide was associated with significantly ($p \leq 0.026$) better outcomes than placebo for all other exacerbation-related endpoints assessed in GLOW2 [31]. Comparisons between the inhaled glycopyrronium bromide and tiotropium bromide arms were not performed for these endpoints. However, reductions in the rate of COPD exacerbation were of similar magnitude in both active treatment arms.

4.5 Effect on Rescue Medication Use

Inhaled glycopyrronium bromide was also associated with significantly ($p \leq 0.039$) less use of rescue medication than placebo, with the least squares mean (LSM) treatment difference (inhaled glycopyrronium bromide vs. placebo) in the change (reduction) from baseline to endpoint in the mean amount of rescue medication used being 0.46 puffs/day at week 26 in GLOW1 [30] and 0.37 puffs/day at week 52 in GLOW2 [31].

Tiotropium bromide was also associated with significantly ($p = 0.003$) less use of rescue medication than placebo in GLOW2, with the treatment difference (tiotropium bromide vs. placebo) for the change from baseline to week 52 in the mean amount of rescue medication used being 0.63 puffs/day [31]. No significant difference in rescue medication use was seen between the inhaled glycopyrronium bromide and tiotropium bromide arms in GLOW2.

4.6 Effect on Exercise Tolerance and Exercise-Related Symptomatology

In GLOW3, inhaled glycopyrronium bromide was associated with a better exercise endurance than placebo after 3 weeks' treatment with regard to the exercise endurance time on day 21 (505.63 vs. 416.7 s; $p < 0.001$ vs. placebo) [primary endpoint] [32]. The between-group difference in exercise endurance time also significantly ($p < 0.001$) favoured inhaled glycopyrronium bromide on day 1 of treatment (490.92 vs. 447.8 s).

Inhaled glycopyrronium bromide was associated with reductions in lung hyperinflation during exercise, with the inspiratory capacity at isotime during a submaximal constant-load cycle ergometry test (SMET) being significantly ($p < 0.001$) higher on days 1 (2.25 vs. 2.02 L) and 21 (2.22 vs. 2.02 L) in patients receiving inhaled glycopyrronium bromide than in those receiving placebo [32]. Isotime was

defined as the last time point in the SMET at which a valid test result in both treatment periods was available; measurements were taken within the last 30 s of each 2-min interval of exercise. The between-group difference in inspiratory capacity just prior to exercise and at peak exercise was also significantly ($p < 0.05$) in favour of inhaled glycopyrronium bromide on both days 1 and 21.

Inhaled glycopyrronium bromide was associated with less leg discomfort on exertion than placebo, with the LSM leg discomfort Borg score being significantly ($p < 0.05$) lower in recipients of inhaled glycopyrronium bromide than in recipients of placebo at isotime on day 21 (6.21 vs. 7.05) [32]; the between-group difference in leg discomfort Borg score was not significant on day 1 (6.67 vs. 7.24).

Scores for the modified Borg dyspnoea scale were significantly ($p < 0.05$) lower in inhaled glycopyrronium bromide than in placebo recipients at isotime on days 1 (6.08 vs. 6.99) and 21 (5.64 vs. 6.8) in GLOW3, indicating that inhaled glycopyrronium bromide was associated with less exertional dyspnoea than placebo [32].

5 Tolerability

The tolerability of inhaled glycopyrronium bromide 50 μg once daily in patients with moderate to severe COPD was assessed over 26 [30] and 52 [31] weeks in the phase III GLOW1 [30] and GLOW2 [31] trials (see Sect. 4 for efficacy data from these trials). Data discussed in this section are mostly from a 6-month safety analysis of pooled tolerability data from GLOW1 and from the first 6 months of GLOW2 that is available in the EMA assessment report for inhaled glycopyrronium bromide [25]. Data from the individual studies [30, 31] or a pooled analysis of 12-month safety data also available in the EMA assessment report [25] are included where appropriate. The 6-month pooled safety analysis included data from 1,877 patients (1,075 of whom received inhaled glycopyrronium bromide) with a median duration of exposure of 182 days, and the 12-month pooled safety analysis included data from 1,060 patients (525 of whom received inhaled glycopyrronium bromide) with a median duration of exposure of 365 days [25].

5.1 General Profile

Overall, inhaled glycopyrronium bromide was generally well tolerated in clinical trials of up to 52 weeks' duration, with most adverse events being mild to moderate in severity [30, 31]. Treatment-emergent adverse events occurred in 59.8 % of inhaled glycopyrronium bromide recipients and 66.7 % of placebo recipients in the 6-month pooled analysis, and in ≈77 % of patients in either group in the 12-month pooled safety analysis [25]. The tolerability profile of inhaled glycopyrronium bromide during 52 weeks' treatment was consistent with the known tolerability profile of the drug [25].

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 % [25]. 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 inhaled glycopyrronium bromide recipients and 30.3 % of placebo recipients during the first 6 months [25].

Adverse events occurring at an incidence of ≥0.5 % in inhaled glycopyrronium bromide recipients and at a ≥1.5-fold higher incidence in inhaled glycopyrronium bromide than placebo recipients were considered to be potentially treatment-related [25]. Of these, dry mouth (see Sect. 5.2 for incidence rates and further discussion), rash (0.93 % of inhaled glycopyrronium bromide recipients vs. 0.37 % of placebo recipients) and extremity pain (0.93 vs. 0.19 %) were the most commonly reported in the 6-month pooled analysis. Inhaled glycopyrronium bromide was not associated with any clinically relevant changes in laboratory values or vital signs [25].

Serious adverse events (SAEs) occurred in 6.98 % of inhaled glycopyrronium bromide recipients and 9.91 % of placebo recipients during the first 6 months, with respective rates over the 12-month period of 12.6 and 16.0 % [25]. Overall, the incidence and nature of SAEs were thought to be consistent with those expected in a population of patients with moderate to severe COPD, with COPD worsening being the most frequently occurring SAE in inhaled glycopyrronium bromide and placebo recipients in the 6-month pooled safety analysis (1.67 vs. 4.3 % of patients), followed by pneumonia (0.56 vs. 1.31 %). Aside from SAEs of atrial fibrillation (AF) [Sect. 5.2], all other SAEs occurred in no more than three inhaled glycopyrronium bromide recipients during the first 6 months. Seven deaths occurred in inhaled glycopyrronium bromide recipients in clinical trials, none of which were thought to be treatment-related [25].

Overall, patient age, gender and race did not appear to affect the tolerability of inhaled glycopyrronium bromide [25]. However, the drug was associated with a numerically higher incidence of headache and urinary tract infection than placebo in elderly patients aged >75 years, but not in those aged ≤75 years [5, 25]. Dosage adjustments in patients aged >75 years are not thought to be necessary [5].

5.2 Specific Adverse Events

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 %) [25]. The majority of cases of dry mouth were reported within the first 4 weeks of treatment and were mild in severity, with none being severe [5]. 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 [5]. All other anticholinergic adverse events occurred at a low frequency (<1.5 % of patients) in both treatment arms [25].

Although the mean change from baseline in QTcF values at most study time points was numerically higher in inhaled glycopyrronium bromide than placebo recipients, the between-group differences were small (≤1.9 ms) and showed an inconsistent pattern [25]. Furthermore, there were no consistent, clinically relevant differences between inhaled glycopyrronium bromide and placebo recipients in the proportion of patients with high QTcF values or with large changes from baseline to endpoint in QTcF values [25].

In the 6-month pooled safety analysis, AF occurred in more inhaled glycopyrronium bromide than placebo recipients (six vs. zero patients) [25]. SAEs of AF occurred in four inhaled glycopyrronium bromide recipients, and three inhaled glycopyrronium bromide recipients prematurely discontinued the study drug because of AF [25]. On further evaluation, the incidence of new or worsening AF on adjudicated ECG recordings was similar between the two treatment arms [25]. In the individual studies, SAEs of AF occurred in three inhaled glycopyrronium bromide recipients over the 26-week treatment period in GLOW1 [30], and in four inhaled glycopyrronium bromide recipients over the 52-week treatment period in GLOW2 [31]. Only one SAE of AF was suspected to be treatment-related [30]. There were no SAEs of AF in the placebo arms of either study [30, 31]. In the 12-month pooled safety analysis, AF caused premature study drug discontinuation in one inhaled glycopyrronium bromide recipient [25].

5.3 Compared with Tiotropium Bromide

The tolerability profile of inhaled glycopyrronium bromide was generally similar to that of tiotropium bromide in terms of the frequency and nature of individual treatment-emergent adverse events and the percentage of patients discontinuing study drug because of adverse events in the 6-month pooled safety analysis [25]. However, with regard to anticholinergic adverse events, dry mouth occurred more frequently in inhaled glycopyrronium bromide than tiotropium bromide or placebo recipients (2.2 vs. 1.5 and 1.1 %), and urinary tract infection occurred less frequently in inhaled glycopyrronium bromide or placebo recipients than in tiotropium bromide recipients (1.8 and 1.9 vs. 3.8 %) [25]. SAEs in both treatment arms were similar in nature and consistent with those expected in a population of patients with moderate to severe COPD [25]. No SAEs of AF occurred in tiotropium bromide recipients in either the 6-month pooled safety analysis [25] or in the 52-week GLOW2 trial [31].

6 Dosage and Administration

Inhaled glycopyrronium bromide is approved in the EU as a long-term maintenance bronchodilator treatment for the symptomatic control of COPD in adult patients [5]. The drug is also approved for use in patients with COPD in various other countries, including Canada [36] and Japan [37].

In the EU, the recommended dosage is the contents of one capsule inhaled once daily, and at the same time each day, using the single-dose Seebri® Breezhaler® inhaler [5]; this is also the maximum recommended dosage [5]. Each capsule contains 63 μg of glycopyrronium bromide, which is equivalent to 50 μg of glycopyrronium, and each delivered dose (i.e. the amount of drug that leaves the inhaler) contains 55 μg of glycopyrronium bromide, which is equivalent to 44 μg of glycopyrronium. Capsules must not be swallowed, and the drug should not be used as an initial treatment for acute bronchospasm.

Because the drug is an anticholinergic agent (see Sects. 2 and 5.2), it should be used with caution in patients with narrow-angle glaucoma or urinary retention [5].

Local manufacturer's prescribing information should be consulted for detailed information, including contraindications, precautions, warnings and use in special populations.

7 Inhaled Glycopyrronium Bromide: Current Status

COPD is a leading cause of morbidity and mortality worldwide, and is a major economic and social burden [1]. Pharmacological therapy does not alter the course of the disease but rather aims to reduce COPD symptom severity, decrease exacerbation frequency and severity, and improve exercise tolerance and other quality-of-life measures [1]. Long-acting bronchodilators, such as LABAs and LAMAs, play a key role in the management of COPD symptoms [1]. Poor adherence to therapy is associated with poor clinical outcomes in COPD [7, 8, 12], and minimizing the dosage frequency is one way in which patient adherence may be improved [7–9].

Inhaled glycopyrronium bromide is approved in various countries, including the EU, as a maintenance bronchodilator for the symptomatic treatment of adult patients with COPD, and is one of few once-daily bronchodilators (besides indacaterol, tiotropium bromide and some formulations of formoterol) approved for this indication in the EU [5]. The efficacy and safety of a once-daily, fixed-dose combination of inhaled glycopyrronium bromide and indacaterol (QVA149) in patients with COPD is also currently being investigated in a large phase III clinical trial programme consisting of ten studies, many of which have already been completed [38–40]. The combination is in the preregistration phase in the EU and Japan [41].

In the pivotal phase III GLOW1 and GLOW2 trials, treatment with inhaled glycopyrronium bromide 50 μg once daily was associated with significantly better lung function than placebo in terms of trough FEV_1 values at 12 weeks (primary endpoint) [Sect. 4.1]. There were also greater improvements in the inhaled glycopyrronium bromide group than in the placebo group in terms of dyspnoea scores (Sect. 4.2), health status (Sect. 4.3), exacerbation rates (Sect. 4.4) and rescue medication use (Sect. 4.5). Furthermore, the benefits of inhaled glycopyrronium bromide over placebo were sustained for up to 52 weeks (Sect. 4). The drug was also associated with better exercise endurance than placebo in terms of the exercise endurance time after 3 weeks' treatment in the phase III GLOW3 trial (Sect. 4.6).

Inhaled glycopyrronium bromide was generally well tolerated in trials of up to 52 weeks' duration, with most adverse events being mild to moderate in severity (Sect. 5.1). SAEs were consistent with those expected in a population of patients with moderate to severe COPD (Sect. 5.1), with only one SAE (an episode of AF) being suspected to be treatment-related (Sect. 5.2). The tolerability profile of inhaled glycopyrronium bromide was generally similar to that of tiotropium bromide in terms of the nature of individual treatment-emergent adverse events and SAEs, and the percentage of patients discontinuing study drug because of an adverse event (Sect. 5.3). Because of concerns relating to the cardiovascular safety of anticholinergic quaternary ammonium compounds, the EMA has requested that the cardiovascular and cerebrovascular safety of inhaled glycopyrronium bromide is monitored in two post-marketing studies: a post-authorisation safety study and a drug utilisation study [25]. A 26-week post-authorisation study evaluating the optimal dosing schedule (i.e. once daily vs. twice daily) for inhaled glycopyrronium bromide was also requested by the EMA [25].

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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. 2011. http://www.goldcopd.org/uploads/users/files/GOLD_Report_2011_Feb21.pdf. Accessed 8 Apr 2013.
2. Hudd TR, Zaiken K. Management of chronic obstructive pulmonary disease: an emphasis on recently approved medications and products in the pipeline. Formulary. 2011;46(9):374–93.
3. Atsou K, Chouaid C, Hejblum G. Variability of the chronic obstructive pulmonary disease key epidemiological data in Europe: systematic review. BMC Med. 2011;9:7.
4. World Health Organization. World health statistics. 2008. http://www.who.int/whosis/whostat/EN_WHS08_Full.pdf. Accessed 8 Apr 2013.
5. Novartis Europharm Ltd. Seebri® Breezhaler® (glycopyrronium bromide) powder for inhalation: EU summary of product characteristics. 2012. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002430/WC500133769.pdf. Accessed 8 Apr 2013.
6. Frampton JE. Aclidinium: in chronic obstructive pulmonary disease. Drugs. 2012;72(15):1999–2011.
7. Bourbeau J, Bartlett SJ. Patient adherence in COPD. Thorax. 2008;63:831–8.
8. Agh T, Inotai A, Meszaros A. Factors associated with medication adherence in patients with chronic obstructive pulmonary disease. Respiration. 2011;82:328–34.
9. 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.
10. Rand CS. Patient adherence with COPD therapy. Eur Respir Rev. 2005;14(96):97–101.
11. Restrepo RD, Alvarez MT, Wittnebel LD, et al. Medication adherence issues in patients treated for COPD. Int J Chron Obstruct Pulmon Dis. 2008;3(3):371–84.
12. 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.
13. 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.
14. Tamura G, Ohta K. Adherence to treatment by patients with asthma or COPD: comparison between inhaled drugs and transdermal patch. Respir Med. 2007;101:1895–902.
15. Cazzola M, Matera MG. Emerging inhaled bronchodilators: an update. Eur Respir J. 2009;34(3):757–69.
16. Novartis Europharm Ltd. Oslif® Breezhaler® (indacaterol) powder for inhalation: EU summary of product characteristics. 2010. http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001210/WC500053307.pdf. Accessed 8 Apr 2013.
17. Boehringer Ingelheim Ltd. Spiriva® (tiotropium bromide monohydrate) powder for inhalation: UK summary of product characteristics. 2012. http://www.medicines.org.uk/EMC/medicine/10039/SPC/Spiriva+18+microgram+inhalation+powder%2c+hard+capsule/. Accessed 8 Apr 2013.
18. Boehringer Ingelheim Ltd. Spiriva® Respimat® (tiotropium bromide monohydrate) solution for inhalation: UK summary of product characteristics. 2012. http://www.medicines.org.uk/

EMC/medicine/20134/SPC/Spiriva+Respimat+2.5+micrograms+solution+for+inhalation/. Accessed 8 Apr 2013.
19. AstraZeneca UK Ltd. Oxis® Turbohaler® 6 (formoterol fumarate dihydrate) powder for inhalation: UK summary of product characteristics. 2010. http://www.medicines.org.uk/EMC/medicine/189/SPC/Oxis+Turbohaler+6%2c+inhalation+powder/. Accessed 8 Apr 2013.
20. AstraZeneca UK Ltd. Oxis® Turbohaler® 12 (formoterol fumarate dihydrate) powder for inhalation: UK summary of product characteristics. 2010. http://www.medicines.org.uk/EMC/medicine/190/SPC/Oxis+Turbohaler+12%2c+inhalation+powder/. Accessed 8 Apr 2013.
21. 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.
22. Haddad E-B, Patel H, Keeling JE. Pharmacological characterization of the muscarinic receptor antagonist, glycopyrrolate, in human and guinea-pig airways. Br J Pharmacol. 1999;127:413–20.
23. Villetti G, Bergamaschi M, Bassani F, et al. Pharmacological assessment of the duration of action of glycopyrrolate vs tiotropium and ipratropium in guinea-pig and human airways. Br J Pharmacol. 2006;148(3):291–8.
24. Casarosa P, Bouyssou T, Germeyer S, et al. Preclinical evaluation of long-acting muscarinic antagonists: comparison of tiotropium and investigational drugs. J Pharmacol Exp Ther. 2009;330(2):660–8.
25. European Medicines Agency. Seebri® Breezhaler® (glycopyrronium bromide): European Medicines Agency assessment report. 2012. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002430/WC500133771.pdf. Accessed 8 Apr 2013.
26. 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.
27. Buhl R, Banerji D. Profile of glycopyrronium for once-daily treatment of moderate-to-severe COPD. Int J Chron Obstruct Pulmon Dis. 2012;7:729–41.
28. 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.
29. Sechaud R, Renard D, Zhang-Auberson L, et al. Pharmacokinetics of multiple inhaled NVA237 doses in patients with chronic obstructive pulmonary disease (COPD). Int J Clin Pharmacol Ther. 2012;50(2):118–28.
30. 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.
31. 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.
32. 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.
33. Fogarty C, Hattersley H, Di Scala L, et al. Bronchodilatory effects of NVA237, a once daily long-acting muscarinic antagonist, in COPD patients. Respir Med. 2011;105(3):337–42.
34. Arievich H, Overend T, Renard D, et al. A novel model-based approach for dose determination of glycopyrronium bromide in COPD. BMC Pulm Med. 2012;12:74.
35. Vogelmeier C, Verkindre C, Cheung D, et al. Safety and tolerability of NVA237, a once-daily long-acting muscarinic antagonist, in COPD patients. Pulm Pharmacol Ther. 2010;23(5):438–44.
36. Novartis Pharmaceuticals Canada Inc. Seebri® Breezhaler® (glycopyrronium bromide) powder for inhalation: Canadian prescribing information. 2012.
37. Novartis. Novartis receives European Commission approval for once-daily Seebri® Breezhaler® as maintenance COPD treatment in the EU. 2012. http://www.novartis.com/newsroom/media-releases/en/2012/1645116.shtml. Accessed 8 Apr 2013.
38. Novartis. Novartis QVA149 phase III study meets primary endpoint in reducing exacerbations in COPD patients, filing in EU and Japan by end of year. 2012. http://www.novartis.com/newsroom/media-releases/en/2012/1637183.shtml. Accessed 8 Apr 2013.
39. Novartis. Novartis data at ERS shows efficacy of once-daily COPD portfolio versus comparators, further establishes dual-bronchodilator QVA149. 2012. http://www.novartis.com/newsroom/media-releases/en/2012/1638207.shtml. Accessed 8 Apr 2013.
40. Novartis. Novartis QVA149 phase III COPD studies meet primary endpoints. 2012. http://www.novartis.com/newsroom/media-releases/en/2012/1599186.shtml. Accessed 8 Apr 2013.
41. The Pharma Letter. Novartis/Vectura's QVA149 is filed as a treatment for COPD in Europe. 2012. http://www.thepharmaletter.com/file/117552/novartisvecturas-qva149-is-filed-as-a-treatment-for-copd-in-europe-certican-eu-approval.html. Accessed 8 Apr 2013.