# Coventry & Warwickshire Area Prescribing Committee

| Drug Positioning Statement | DPS066 |
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| **Glycopyrronium bromide/indacaterol maleate (Ultibro® Breezhaler®) [Treatment of COPD]** | **May 2016** |

## VERDICT

The Coventry & Warwickshire Area Prescribing Committee approves the prescription of this combination inhaler product but will review this decision once new NICE guidance has been published in due course.

**VERDICT:** Ultibro® Breezhaler® is recommended as an alternative for the treatment of COPD and is not classed as specialist

## SUMMARY NOTES

**Indication:** Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

**Pharmacological action[1]:** Indacaterol is a long-acting beta$_2$-adrenergic agonist; glycopyrronium is an inhaled long-acting muscarinic receptor antagonist (anticholinergic), for once-daily maintenance bronchodilator treatment of COPD.

**Presentation[1]:** Each capsule contains 143 micrograms indacaterol maleate equivalent to 110 micrograms of indacaterol and 63 micrograms of glycopyrronium bromide equivalent to 50 micrograms of glycopyrronium.
Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 110 micrograms of indacaterol maleate equivalent to 85 micrograms of indacaterol and 54 micrograms of glycopyrronium bromide equivalent to 43 micrograms of glycopyrronium.

**Dose[1]:** The recommended dose is the inhalation of the content of one capsule once daily using the Ultibro® Breezhaler® device.

**Cost comparison: 30 days treatment (these doses do not imply therapeutic equivalence and are merely for comparison)[2]**

**LAMA+LABA combinations**

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|---|---|---|---|
| **Indacaterol+ glycopyrronium (Ultibro®** Breezhaler®) | **85/43 micrograms** | **1 puff daily** | **£36.88** |
| Umeclidinium + Vilanterol (Anoro® Ellipta®) | 55/22 micrograms | 1 puff daily | £32.50 |
| Aclidinium/formoterol (Duaklir® Genuair®) | 340/12 micrograms | 1 puff bd | £32.50 |

**LAMAs**

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|---|---|---|---|
| Umeclidinium (Incruse® Ellipta®) | 55 micrograms | 1 puff daily | £27.50 |
| Aclidinium (Eklira® Genuair®) | 322 micrograms | 1 puff bd | £28.60 |
| Glycopyrronium (Seebri® Breezhaler®) | 44 micrograms | 1 puff daily | £27.50 |
| Tiotropium (Spiriva® Handihaler®) | 18 micrograms | 1 puff daily | £33.50 |
| Tiotropium (Spiriva® Respimat®) | 2.5 micrograms | 2 puffs daily | £33.50 |

**LABAs**

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|---|---|---|---|
| Indacaterol (Onbrez Breezhaler®) | 150/300 micrograms | 1 puff daily | £29.60 |
| Formoterol (Easyhaler®) | 12 micrograms | 1 puff bd | £11.88 |
| Olodaterol (Striverdi® Respimat®) | 2.5 micrograms | 2 puffs daily | £26.35 |
| Salmeterol (Serevent® Evohaler® ) | 25 micrograms | 2 puffs bd | £29.26 |

**Combination ICS/LABA**

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|---|---|---|---|
| Beclometasone/Formoterol (Fostair® MDI) | 100/6 micrograms | 2 puffs bd | £29.32 |
| Budesonide/ Formoterol (Symbicort® Turbohaler®) | 400/12 micrograms | 1 puff bd | £38.00 |
| Fluticasone propionate/salmeterol (Seretide® Accuhaler®) | 500/50 micrograms | 1 puff bd | £40.92 |
| Fluticasone furoate/vilanterol (Relvar® Ellipta®) | 92/22 micrograms | 1 puff daily | £27.80 |

**Clinical Effectiveness**

Key randomised controlled trials (RCTs) are evaluated in the NICE evidence summary. The RCTs were multicentre (including UK), patients were aged 40 years or over and were current or ex-smokers with a smoking history of at least 10 pack years[3]. Patients with certain cardiovascular conditions were excluded from clinical trials[1].

Two studies have reported lung function measures at week 26 as primary outcomes: SHINE (n=2144) and ILLUMINATE (n=523).

In SHINE, in patients with moderate or severe stable COPD, indacaterol/glycopyrronium statistically significantly improved trough $FEV_1$ compared with indacaterol, glycopyrronium, open-label tiotropium and placebo (LSM differences 70 ml, 90 ml, 80 ml and 200 ml respectively; p<0.001 in all comparisons)[3]. Patients using fixed-dose ICS/LABA at study entry were switched to an equivalent dose of ICS monotherapy. Most patients (75%) did not report any exacerbations in the previous year. For comparisons with active comparators, these changes in $FEV_1$ are less than the 100 ml or more than the full NICE guideline on COPD considers to be clinically important.

In the other study, ILLUMINATE, patients had a history of moderate or severe stable COPD, Patients with a history of a COPD exacerbation needing treatment with antibiotics, systemic corticosteroids or hospitalisation in the previous 12 months were excluded. Long-acting COPD maintenance therapy (LAMAs, LABAs, ICS and LABA/ICS) was withdrawn in a washout period. The $FEV_1$ standardised area under the curve from 0 to 12 hours ($FEV_1$ $AUC_{0\text{-}12h}$) at week 26 was significantly higher with indacaterol/glycopyrronium compared with salmeterol/fluticasone (LSM difference 138 ml, 95% CI 100 ml to 176 ml; p<0.0001).

SPARK and BLAZE studies reported exacerbations and dyspnoea as their primary outcomes. In these 2 studies, treatment with ICS was continued and patients using combined LABA/ICS were switched to equivalent ICS monotherapy.

In SPARK (n=2224), indacaterol/glycopyrronium statistically significantly reduced the annualised rate of moderate to severe exacerbations in people with severe or very severe COPD by 12% compared with glycopyrronium alone ([RR] 0.88, 95% [CI] 0.77 to 0.99, p=0.038). A non-significant reduction of 10% was seen in this outcome between indacaterol/glycopyrronium and open-label tiotropium (RR 0.90, 95% CI 0.79 to 1.02, p=0.096). In the European public assessment report for indacaterol/glycopyrronium, the 12% reduction was considered to be 'very small' and not supportive of the manufacturer's requested indication of 'exacerbation reduction'[4]. The full NICE guideline on COPD considers a relative reduction in the risk of exacerbations of 20% or more to be clinically important[5].

BLAZE (n=247) found that indacaterol/glycopyrronium statistically significantly improved dyspnoea scores in people with moderate or severe COPD compared with placebo. The mean difference exceeded the 1 point improvement considered to be clinically important (least squares mean [LSM] difference 1.37, 95% CI 0.95 to 1.79; p<0.001)[5]. The dyspnoea score for indacaterol/glycopyrronium was also statistically significantly higher than for tiotropium (LSM difference 0.49, 95% CI 0.07 to 0.91; p=0.021). However, this difference is unlikely to be clinically important[5].

**Adverse effects**

The SPC reports that up to 15 months' treatment with indacaterol/glycopyrronium showed similar adverse reactions to those observed when people were treated with each drug individually. The most common side effect (very common, affecting at least 10% of patients) is upper respiratory tract infection[1].

The 52-week safety study (ENLIGHTEN; n=339) found that the incidence of adverse events was similar in the indacaterol/glycopyrronium and placebo groups (57.8% and 56.6% respectively; p value not reported). Thirteen people receiving indacaterol/glycopyrronium (5.8%) had an adverse event leading to discontinuation of the study drug compared with 7 people receiving placebo (6.2%; p value not reported)[3].The safety profile is characterised by typical anticholinergic and beta-adrenergic symptoms related to the individual components of the combination. Other most common adverse reactions related to the product (reported in at least 3% of patients for indacaterol/glycopyrronium Breezhaler® and also greater than placebo) were cough and oropharyngeal pain (including throat irritation)[1,3].

**Renal impairment/Hepatic impairment/Elderly**

**Elderly:** No dosage adjustment in elderly patients (75 years of age and older).
**Renal impairment:** Indacaterol/glycopyrronium can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis it should be used only if the expected benefit outweighs the potential risk.
**Hepatic impairment:** It can be used at the recommended dose in patients with mild and moderate hepatic impairment. There are no data available for the use of Indacaterol/glycopyrronium in patients with severe hepatic impairment, therefore caution should be observed in these patients.

**Cautions and contra-indications**

Indacaterol/glycopyrronium should not be used for the treatment of asthma due to the absence of data in this indication[1].

No data are available in patients with narrow-angle glaucoma or urinary retention, therefore indacaterol/glycopyrronium should be used with caution in these patients. Indacaterol/glycopyrronium should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension). 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 whose QTc (Fridericia method) was prolonged (>450 ms) were *excluded* from the clinical trials, and therefore there is no experience in these patient groups; caution should be used in these groups[1]. It should be used with caution in patients with convulsive disorders or thyrotoxicosis.

## DRUG PROFILE cont'd

Hypokalaemia, in line with beta$_2$-adrenergic agonists, may occur which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta$_2$-adrenergic agonists, therefore use with caution[1].

Inhalation of high doses of beta$_2$-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment plasma glucose should be monitored more closely in diabetic patients[1].

## CURRENT PLACE IN THERAPY

**National institute for Health and Care Excellence (NICE)**
NICE states that the use of dual therapy with a LAMA and LABA may be considered if an inhaled corticosteroid (ICS; as part of combination therapy with a LABA) is declined or not tolerated. NICE developed these recommendations in 2010, which predates the publication of the evidence for the newer LABAs and LAMAs[5]. An update to the guideline is expected in June 2016.

**The Global initiative for chronic obstructive lung disease (GOLD)**
GOLD recommends the combined use of LAMA and LABA as an option in patients who have a low risk of exacerbation but have significant symptoms with monotherapy. GOLD also recommends a LAMA + LABA combination as an alternative option to combined ICS with LABA or LAMA, which are generally used in patients with few symptoms but a high risk of exacerbations. For patients with many symptoms and a high risk of exacerbations, the combination of ICS, LAMA and LABA is a second choice option[6].

**Scottish Medicines Consortium (SMC)**
Indacaterol maleate plus glycopyrronium bromide inhalation powder hard capsules (Ultibro® Breezhaler®) is accepted for use within NHS Scotland in patients for whom the combination of the two ingredients is appropriate as the combination product has a lower cost than the individual components[7].

**Summary**

- Indacaterol/ glycopyrronium is supplied in single-use dry powder capsules using a dry powder inhaler, the Breezhaler®
- Indacaterol/glycopyrronium showed a small improvement in lung function compared with active comparators (indacaterol, glycopyrronium, tiotropium and fluticasone/salmeterol) in people with moderate to very severe COPD for up to 52 weeks. Indacaterol/glycopyrronium also showed small improvements in dyspnoea, health status and use of rescue medication compared with active comparators. These improvements are of uncertain clinical benefit[3].
- Indacaterol/glycopyrronium reduced the rate of moderate or severe exacerbations compared with glycopyrronium alone in people with severe or very severe COPD. However, the EMA considered that the reduction was insufficient to support an indication for reducing exacerbations[3]. There is no data on hospitalisation rates and no safety data beyond 18 months[8].
- Compared with established drugs such as formoterol, salmeterol and tiotropium, the comparative efficacy and long-term safety of indacaterol and glycopyrronium (alone or in combination) is unclear, particularly in terms of reducing exacerbations[3]. A further 52 week trial evaluating indacaterol/glycopyrronium against Seretide®accuhaler with exacerbation rate as the primary outcomes is expected to complete September 2015[9].
- GOLD guidelines, updated in January 2015, state that whilst combinations of a long-acting beta$_2$-agonist and a long-acting anticholinergic have shown a significant increase in lung function, the impact on patient reported outcomes is still limited. There is still too little evidence to determine if a combination of long-acting bronchodilators is more effective than a long-acting anticholinergic alone for preventing exacerbations[6].
- Whilst NICE states that the current place in therapy of a combination LAMA/LABA is unclear, the guidelines also states that use of dual therapy with a LAMA and LABA may be considered if an ICS (as part of combination therapy with a LABA) is declined or not tolerated[6].
- Specialists involved in producing the NICE evidence summary consider that indacaterol/glycopyrronium may be used to relieve symptoms in people with COPD who remain symptomatic on a LABA or LAMA. However, current evidence does not support the use of indacaterol/ glycopyrronium to reduce exacerbations in people with COPD, either as an intermediate step between LAMA monotherapy and LAMA plus LABA/ICS triple therapy, or as an alternative to LABA/ICS[3].
- The indacaterol/glycopyrronium combination is less expensive than individual components. The APC does not recommend indacaterol alone in any setting.

**References**


1. Summary of product characteristics (Indacaterol/glycopyrronium Breezhaler®), Date of revision of text 3/2/2015 Available from www.medicines.org.uk <Accessed 6/3/15>
2. DM & D available from http://195.59.176.218/dmd_download.htm <Accessed 10/02/15>
3. NICE evidence summary. ESNM33: Chronic obstructive pulmonary disease: indacaterol/glycopyrronium (Indacaterol/glycopyrronium Breezhaler). Available from http://www.nice.org.uk/advice/esnm33 <accessed 23/04/15>
4. European Medicines Agency assessment report. Indacaterol/glycopyrronium® Breezhaler October 2013 Available via http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002679/human_med_001691.jsp&mid=WC0b01ac058001d124 <Accessed 23/04/2015>
5. National Institute for Health and Care Excellence (NICE). Clinical Guideline, CG 101. Chronic Obstructive Pulmonary Disease (updated) June 2010. Available via http://guidance.nice.org.uk/CG101 <Accessed 23/04/2015>
6. Global Initiative for Chronic Obstructive lung disease (GOLD), Management and prevention of COPD. January 2015. Available via www.goldcopd.com <Accessed 23/04/2015>
7. Scottish Medicines Consortium indacaterol maleate, glycopyrronium bromide (Indacaterol/glycopyrronium Breezhaler). SMC ID 922/13 Available from http://www.scottishmedicines.org.uk/SMC_Advice/Advice/index <accessed 23/4/15>
8. London Medicines Evaluation Network Review. Indacaterol/glycopyrronium Breezhaler® (indacaterol/glycopyrronium) - Maintenance bronchodilator treatment to relieve symptoms in adults with COPD February 2014. Available via http://www.medicinesresources.nhs.uk/upload/Indacaterol/glycopyrronium_finalFeb2014.pdf
9. Midlands Therapeutic Review and Advisory Committee (MTRAC) Commissioning Support. Fixed dose LABA/LAMA inhalers for the treatment of chronic obstructive airways disease (COPD). March 2015