For patients with COPD who are symptomatic with breathlessness and have exacerbations, in spite of monotherapy with either a LABA or LAMA then NICE guidance on the management of COPD recommends that a combination of a long-acting antimuscarinic agent (LAMA) and a long-acting beta agonist (LABA) can be used. The combination also may be used for patients who cannot tolerate inhaled steroids. There are now three such combinations in a single inhaler – aclidinium/formoterol (Duaklir Genuair), umeclidinium/vilanterol (Anoro Ellipta) and glycopyrronium/indacaterol (Ultibro Breezhaler), each utilising a different device.

**Ultibro Breezhaler**

Ultibro Breezhaler is a fixed dose inhaler combining the LAMA glycopyrronium bromide 43µg (available in a 44µg dose as Seebri Breezhaler) and indacaterol 85µg (available in a 120µg dose as Onbrez Breezhaler). The Breezhaler is a dry powder inhaler in which a capsule is loaded into the device for each dose. Ultibro is licensed for maintenance treatment to relieve symptoms in adults with COPD. The recommended dose is one capsule once daily.

As with other LAMAs, the way the dose is expressed is potentially confusing. A capsule contains indacaterol maleate 143µg (equivalent to 110µg indacaterol) and glycopyrronium bromide 63µg (equivalent to 50µg glycopyrronium). The delivered dose from the inhaler contains indacaterol maleate 110µg (equivalent to 85µg indacaterol) and glycopyrronium bromide 54µg (equivalent to 43µg).

No adjustment is recommended for older people or patients with mild or moderate renal or hepatic impairment. The balance of benefit and risk should be assessed in patients with severe renal impairment; there are no data on its use in patients with severe hepatic impairment. Ultibro shares with the prescribing cautions, contraindications and drug interactions of other LAMAs and LABAs.

**Clinical trials**

Glycopyrronium/indacaterol has been compared with fluticasone/salmeterol in patients with moderate to severe COPD.\(^2\) Trials comparing glycopyrronium/indacaterol with component monotherapy drugs or tiotropium have been evaluated in a systematic review.\(^3\)

A total of 523 patients with moderate to severe COPD (80 per cent moderate), but no exacerbations in the previous year, were randomised to treatment with glycopyrronium/indacaterol once daily or salmeterol/fluticasone 50/500µg twice daily.\(^2\) The primary endpoint was lung function (FEV\(_1\), standardised area under the curve from 0 to 12 hours, FEV\(_1\) \(\text{AUC}_{0-12h}\)) at week 26.
Lung function was significantly greater with glycopyrronium/indacaterol than salmeterol/fluticasone at 26 weeks and the difference was clinically meaningful (see Figure 1). The LAMA/LABA combination as also superior for other spirometry end-points but there was no significant difference in health related quality of life score (St George’s Respiratory Questionnaire). Breathlessness score (Transition Dyspnoea Index, TDI) was significantly improved but the difference was below what is considered as clinically meaningful (1.0 unit change). The proportion of patients with a change in TDI score ≥1.0 by 26 weeks was significantly higher with glycopyrronium/indacaterol (66 vs 59 per cent). Use of rescue salbutamol was significantly lower with glycopyrronium/indacaterol by an average of 0.4 puffs per day.

The systematic review included five trials lasting 3–64 weeks and a total of 4842 patients with stable moderate to severe COPD (36 per cent moderate, 10 per cent very severe). Compared with tiotropium, the LAMA/LABA combination significantly increased FEV₁, though the mean difference was 70ml, below the clinically meaningful threshold of 100ml. It was also associated with statistically but not clinically significant improvements in SGRQ and TDI scores over tiotropium and reduced average rescue salbutamol use by 0.6 puffs per day. There were similar improvements over monotherapy with glycopyrronium or (in one trial) indacaterol. Overall, about 10 per cent more patients experienced a clinically meaningful improvement in SGRQ score with glycopyrronium/indacaterol combined.

Adverse effects
The adverse events reported with glycopyrronium/indacaterol are typical of its component drugs, the most frequent being cough and oropharyngeal pain.

Place in therapy
There is currently no evidence of clinically important differences between the new LAMA/LABA inhalers and the choice between them may therefore depend on patient preference for dose frequency and type of inhaler, and cost. To that extent, Ultibro Breezhaler extends patient choice, though there is little useful data as to which device (Breezhaler, Ellipta or Genuair) is preferred. Combined therapy offers a small overall improvement in patient outcomes compared with monotherapy with a component drug but individual patients may derive greater benefit.

References
1. NICE. Inhaled therapy in COPD. December 2014.

Declaration of interests
None to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics

share your views
If you have any issues you would like to air with your colleagues or comments on articles published in Prescriber, the editor would be pleased to receive them and, if appropriate, publish them on our forum page. Please send your comments to:
The editor, Prescriber, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, or e-mail to prescriber@wiley.com

data are least squares mean (SE)
SFC=salmeterol-fluticasone; *p<0.0001 for comparison between glycopyrronium/indacaterol and SFC

Figure 1. Glycopyrronium/indacaterol vs salmeterol/fluticasone. Lung function (FEV₁, standardised area under the curve from 0 to 12 hours, FEV₁AUC₀–₁₂h) at week 26.²

Data are least squares mean (SE)
SFC=salmeterol-fluticasone; *p<0.0001 for comparison between glycopyrronium/indacaterol and SFC

Share your views
If you have any issues you would like to air with your colleagues or comments on articles published in Prescriber, the editor would be pleased to receive them and, if appropriate, publish them on our forum page. Please send your comments to:
The editor, Prescriber, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, or e-mail to prescriber@wiley.com

prescriber.co.uk

Prescriber 19 April 2015