



# Commissioning Support

Extrafine beclometasone dipropionate  
87 mcg, formoterol fumarate 5 mcg,  
and glycopyrronium bromide 9 mcg  
(*Trimbow*<sup>®</sup>)

## For maintenance treatment of Chronic Obstructive Pulmonary Disease

### Commissioning guidance:

Commissioners may wish to bear the following in mind when considering the commissioning of Trimbow:

- The need for accurate diagnosis and identification of the disease severity as moderate to severe.
- The need for accurate recording of the patient's diagnosis and exacerbation history through use of a standard form, such as the COPD Assessment Test.<sup>1</sup>
- Local guidance advises consideration of the patient's eligibility for pulmonary rehabilitation, as well as other measures such as smoking cessation and a flu vaccination as part of the management of COPD.<sup>2</sup>
- In patients who need the triple combination of ICS/LABA/LAMA (inhaled corticosteroid/long-acting beta agonist/long-acting muscarinic antagonist), there may be benefit in terms of increased patient convenience and compliance with the use of a single inhaler instead of two.
- There is a lower 30-day acquisition cost associated with the use of the triple inhaler compared with the use of two inhalers to deliver ICS/LABA + LAMA.

### Strength of the evidence for efficacy:

One phase III double-blind randomised controlled trial (TRINITY RCT) showed that the triple combination of beclometasone dipropionate, formoterol fumarate dihydrate and glycopyrronium bromide in a single Trimbow inhaler was non-inferior in terms of exacerbation rate and quality of life than a combination of ICS/LABA (Fostair: beclometasone dipropionate 100 mcg/formoterol fumarate 6 mcg) + LAMA (tiotropium 18 mcg) administered as two separate inhalers. Two further trials showed that Trimbow treatment resulted in fewer exacerbations (primary outcome in TRIBUTE and secondary outcome in TRILOGY), and greater improvement in quality of life than the Fostair dual combination inhaler (TRIBUTE) and the Ultibro Breezhaler (TRILOGY).

*MTRAC considered Trimbow because it was a new licensed product that primary care prescribers may be asked to prescribe.*

### Description of technology

Trimbow (contains: beclometasone dipropionate 87 mcg/formoterol fumarate dihydrate 5 mcg/glycopyrronium bromide 9 mcg per delivered dose) is licensed for maintenance treatment in adult patients with moderate to severe COPD who are not adequately treated by a combination of an ICS and a LABA. Trimbow is delivered via a pressurised metered dose inhaler (pMDI); the recommended dose is two inhalations, twice daily. See the Summary of Product Characteristics (SPC) for full details of this product.<sup>3</sup>

### Background

COPD is a common inflammatory disease characterised by persistent respiratory symptoms and pulmonary airflow obstruction that is usually progressive and not fully reversible.<sup>4</sup> It is a common cause of long-term disability and death that presents a major burden to healthcare services.

There are estimated to be over 3 million people with COPD in the UK.<sup>5</sup> Quality and outcomes framework (QOF) data for 2016/17 show that the mean prevalence of diagnosed COPD in the West Midlands (NHS England region) is 1.86% (74,366 patients).<sup>6</sup>

Current guidance advises that triple therapy with an ICS/LABA + LAMA is recommended for use in people with moderate to severe COPD who have continued

breathlessness and exacerbations despite treatment with an ICS/LABA combination or LAMA (GOLD category D: high risk of exacerbations, more symptoms).<sup>2,4,7</sup>

### Clinical evidence for efficacy and safety

Three fully published, phase III, double-blind, multicentre RCTs (TRIBUTE, TRINITY and TRILOGY) evaluated fixed-dose triple therapy with Trimbow (two puffs, twice daily) in adults with COPD.<sup>8-10</sup> All patients in the trials had received treatment with an ICS/LABA, LABA/LABA or LAMA inhaled therapy for at least 2 months before trial entry, and had suffered an exacerbation in the previous year. The trials were of 52 weeks' duration.

The primary outcome in the TRIBUTE (n = 1,532)<sup>8</sup> and TRINITY trials (n = 2,691)<sup>10</sup> was an evaluation of the rate of moderate to severe exacerbations in patients receiving Trimbow twice daily. Comparators were tiotropium 18 mcg once daily in the TRINITY trial (and an 'open triple' combination; see below), or the Ultibro Breezhaler once daily (indacaterol 110 mcg/glycopyrronium bromide 50 mcg) in the TRIBUTE trial. Selected secondary outcomes included the times to first moderate-to-severe and severe exacerbations following trial enrolment. Other outcomes included measures of lung function and quality of life, using the St George's



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respiratory questionnaire (SGRQ).

In the TRINITY trial, comparators were tiotropium (18 mcg once daily, delivered via Spiriva Handihaler) and an 'open triple' therapy group where participants received a combination of ICS/LABA + LAMA via two inhalers (beclometasone dipropionate 100 mcg/formoterol fumarate 6 mcg [Fostair; 2 inhalations twice daily] + tiotropium 18 mcg once daily). The trial found that there was no significant difference for outcomes between the fixed (Trimbow) and open (Fostair + tiotropium) triple therapy groups. Compared with tiotropium, both triple therapy groups showed a significantly lower rate of moderate-to-severe exacerbations (exacerbation rate/year in the Trimbow group was 0.46 vs. 0.57 in the tiotropium group; adjusted Rate Ratio 0.80 [95% Confidence Interval [CI] 0.69 to 0.92];  $p = 0.0025$ ), and a longer time to either the first moderate-to-severe exacerbation or severe exacerbation. Other secondary outcome measures showed significantly greater improvements in lung function (forced expiratory volume in one second; FEV<sub>1</sub>) with both triple therapies vs. tiotropium monotherapy, and a greater improvement in SGRQ scores: 46% of the Trimbow triple therapy group achieved a clinically significant improvement of  $\geq 4$  points compared with 39% of people receiving tiotropium ( $p = 0.0019$ ).<sup>10</sup>

The TRIBUTE trial<sup>8</sup> compared Trimbow with a LABA/LAMA (Ultibro Breezhaler) over 52 weeks' treatment, and found a significantly lower rate of moderate-to-severe exacerbations with Trimbow vs. Ultibro. Adjusted rates were 0.50 per patient per year (95% CI 0.45 to 0.57) for patients receiving Trimbow and 0.59 (0.53 to 0.67) per patient per year for those receiving Ultibro; adjusted rate ratio of 0.848 (95%CI 0.723 to 0.995;  $p=0.043$ ). There was no significant difference between treatment groups for the time to first moderate or severe exacerbation, or time to first severe exacerbation. The improvement in mean SGRQ score over the treatment period was significantly greater with Trimbow vs. Ultibro but there was no significant difference in the numbers of participants showing a response to treatment (41% for Trimbow vs. 36% for Ultibro; odds ratio [OR] 1.22; 95% CI 0.99 to 1.51;  $p = 0.068$ ). There was also no significant difference in the proportion of patients showing an improvement in lung function (19% vs. 16%; OR 1.19; 0.91 to 1.55;  $p = 0.198$  [improvement defined as  $\geq 100$  mL increase from baseline]).

The TRILOGY trial ( $n = 1,368$ )<sup>9</sup> used the same inclusion and exclusion criteria as TRIBUTE and TRINITY, but the primary outcomes were measures of lung function (FEV<sub>1</sub>) and breathlessness (transition dyspnoea score; TDI) after 26 weeks' treatment. The comparator was the dual combination ICS/LABA Fostair inhaler (two puffs, twice daily). There were significantly greater improvement in pre-dose and 2h post-dose FEV<sub>1</sub> at all clinic visits for Trimbow vs. Fostair, and a greater proportion of participants had an improvement of at least 0.1 L in their pre-dose FEV<sub>1</sub> with Trimbow vs. dual

ICS/LABA Fostair therapy (after 52 weeks: 38% vs. 23%;  $p < 0.001$ ). Participants receiving Trimbow were significantly more likely to have a clinically relevant improvement in SGRQ total score (47% and 43% after 26 and 52 weeks' treatment, respectively in the Trimbow group vs. 36% in the dual therapy group at both weeks 26 and 52). A lower percentage of patients in the Trimbow group had a moderate-to-severe exacerbation compared with Fostair (31% vs. 35% in the Fostair group).<sup>9</sup> The adjusted annual rate of moderate-to-severe exacerbations was 0.41 for the Trimbow group, and 0.53 for the Fostair group, with a rate ratio of 0.77 (95% CI 0.65 to 0.92;  $p=0.005$ ).

### Adverse events

Across the trials, about 55% of participants had treatment emergent adverse events with Trimbow; with similar findings reported for the comparator groups. The most frequent were exacerbation of COPD (reported in 31-33% in the Trimbow groups), nasopharyngitis (5-6%), pneumonia (3%), and headache (2-4%). See the SPC for full details of all contraindications and adverse events.<sup>3</sup>

### Considerations for cost impact

The current prices of the new triple therapy combined inhalers are below (yearly cost, excluding VAT; Source MIMs Online, [August 2018](#)):

- Trimbow (2 inhalations, twice daily; pMDI) £541.42
- Trelegy Ellipta<sup>▼</sup> (1 inhalation, once daily; DPI\*) £541.42  
\*Dry powder inhaler

### References

1. COPD Assessment Test. GlaxoSmithKline Services Unlimited 2016 <http://www.catestonline.org/>
2. [Turner A. Diagnosis and management of stable COPD. Pan Birmingham Respiratory Clinical Network 2017](#)
3. [Chiesi Ltd. Trimbow 87 micrograms/5 micrograms/9 micrograms pressurised inhalation, solution. EMC 2017](#)
4. [Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease \(GOLD\) 2018. Global Initiative for Chronic Obstructive Lung Disease 2018](#)
5. [An Outcomes Strategy for COPD and Asthma: NHS Companion Document. Department of Health 2012](#)
6. [QOF 2016/17 results. NHS Digital 2017](#)
7. [Chronic obstructive pulmonary disease in over 16s: diagnosis and management \(CG101\). NICE 2016](#)
8. Papi A et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet* 2018; 391(10125):1076-1084.
9. Singh D et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting beta2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2016; 388(10048):963-973.
10. Vestbo J et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2017; 389(10082):1919-1929.

**WARNING:** This sheet should be read in conjunction with the Summaries of Product Characteristics

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.



**Keele University** Centre for Medicines Optimisation