New Medicine Recommendation
Trimbow

Beclometasone / formoterol / glycopyrronium bromide pressurised metered dose inhaler for treatment of COPD

Recommendation: GREEN (restricted)

Restriction: Triple therapy should be reserved for patients who have failed to achieve or maintain an adequate response to an appropriate course of dual therapy.

Appropriate for initiation and ongoing prescribing in both primary and secondary care.

Generally, little or no routine drug monitoring is required

Summary of supporting evidence

- **TRILOGY** shows that in patients with COPD who have severe or very severe airflow limitation, symptoms, and an exacerbation history, triple therapy with BDP/FF/GB (beclometasone dipropionate / formoterol fumarate / glycopyrronium bromide) had a greater effect on pre-dose and 2-h post-dose FEV1 than BDP/FF. For the co-primary endpoint measuring breathlessness (Transition Dyspnea Index, TDI), superiority of BDP/FF/GB over BDP/FF was not shown. The rate of moderate-to-severe COPD exacerbations was 23% lower with BDP/FF/GB compared with BDP/FF, with the time to first exacerbation significantly longer with triple therapy. Thus, the greater improvement in lung function with BDP/FF/GB compared with BDP/FF was more clearly accompanied by a reduction in exacerbations than an improvement in breathlessness in this group of patients. Furthermore, BDP/FF/GB had a greater effect on health related quality of life than BDP/FF.
- **TRINITY** met the primary and both key secondary endpoints. Extrafine fixed triple (i.e. extra fine inhaled particle fraction, ICS/LABA/LAMA in one inhaler) resulted in a 20% (95% CI 8–31) reduction in the rate of moderate-to-severe COPD exacerbations compared with tiotropium, together with a 0·061L mean improvement in pre-dose FEV1. Furthermore, the non-inferiority of fixed triple relative to open triple (ICS/LABA +LAMA in two inhaler devices) was shown for pre-dose FEV1. Fixed triple reduced both moderate and severe exacerbation rates, hyperinflation (as measured by inspiratory capacity), and rescue medication use, with more St. George's Respiratory Questionnaire (SGRQ) responders compared with tiotropium, and effects generally similar to open triple.

Caveats to evidence

- **TRILOGY** - used inhaled corticosteroid (ICS) and long-acting β_2-agonist treatment (LABA) as the comparator group, GOLD 2017 now recommends use of LABA +LAMA in preference to LABA +ICS for the treatment of COPD patients. Therefore, most COPD patients will progress to triple therapy from LABA +LAMA, so comparator arm bears little relevance to current clinical practice / recommendations. This was acknowledged by the study authors - “Our study did not address the benefit of escalation to triple therapy from a long-acting β_2-agonist/long-acting muscarinic antagonist combination. This is an important point to examine in the future, especially given that a study suggested that long-acting β_2-agonist/long-acting muscarinic antagonist treatment is more effective on a wide range of endpoints including exacerbations than an inhaled corticosteroid/long-acting β_2-agonist combination.”
- The 23% reduction in the exacerbation rate, which is above the suggested minimum clinically

important difference, can be attributed to the long-acting muscarinic antagonist (LAMA) component of BDP/FF/GB.

- Patients already on triple therapy (as two separate inhalers) were excluded from the study and so no direct comparison can be made.
- A Cochrane review recently concluded that for the treatment of COPD, LAMA+LABA has fewer exacerbations compared to ICS+LABA, a larger improvement of FEV1, a lower risk of pneumonia, and more frequent improvement in quality of life as measured by an increase over 4 units or more of the SGRQ. These data were supported by low or moderate quality evidence generated from mainly participants with moderate to severe COPD in heterogeneous trials with an observation period of less than one year- findings support the recently updated GOLD guidance.
- **TRINITY** – does not answer the question of the value of adding an inhaled corticosteroid to a long-acting β_2-agonist plus long-acting muscarinic antagonist combination, even though this is now the recommended treatment option.
- Patients being treated as per GOLD 2017 guidelines would not progress from treatment with a long acting muscarinic antagonist (tiotropium) to triple therapy, but instead would progress to treatment with a long-acting β_2-agonist/long-acting muscarinic antagonist combination.
- Patients already on triple therapy (as two separate inhalers) were excluded from the study and so no direct comparison can be made.
- Patients received tiotropium (LAMA) for run in period (irrespective of their current treatment – majority of patients on dual therapy pre study and therefore this represents a step down in treatment), but were then escalated to treatment with triple therapy – this would not happen in current clinical practice.
- Majority of study patients were on ICS /LABA therapy at study entry which is not representative of the currently recommended clinical treatment pathway.
- The fixed triple therapy provided similar results to the open triple therapy.
- Lower than expected exacerbation rates were observed in all three groups.

Details of Review

Name of medicine (generic & brand name): Trimbow[1] Beclometasone / formoterol / glycopyrronium bromide
Strengths and forms: A pressurised metered dose inhaler delivering a solution with a nominal dose per actuation of 87 micrograms / 5 micrograms / 9 micrograms of the active substances respectively. Available as 120 actuation pressurised container.
Dose and administration: Adults - The recommended dose is two inhalations of Trimbow twice daily. The maximum dose is two inhalations of Trimbow twice daily.
BNF therapeutic class / mode of action: Chapter 3: 1, Airways disease, obstructive Trimbow is a triple combination of an inhaled glucocorticoid (beclometasone dipropionate), a long-acting beta$_2$ receptor agonist (formoterol fumarate dihydrate) and a long-acting muscarinic antagonist (glycopyrronium bromide). Beclometasone reduces inflammation in the lungs, whereas formoterol and glycopyrronium produce relaxation of bronchial smooth muscle helping to dilate the airways and make breathing easier.

Licensed indication(s):

Maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta$_2$-agonist.

Proposed use:

Within licensed indication

Course and cost:

Ongoing maintenance treatment.

NHS list price is £44.50 per 120 actuation device (equates to 30 days treatment on recommended dose).

Current standard of care/comparator therapies:

The use of inhaled triple pharmacologic therapy by patients with chronic obstructive pulmonary disease (COPD) is common; a UK study found that after 2 years, 46% of patients initially prescribed a long-acting bronchodilator and 39% of those prescribed an inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) or ICS plus long-acting muscarinic antagonist (LAMA) progressed to triple therapy.[2]

However, the Global Initiative for Chronic Obstructive Lung Disease strategy document[3] recommends inhaled triple pharmacologic therapy (ICS/LAMA/LABA) only for patients with advanced COPD with persistent symptoms and risk of exacerbations but up to now , no single inhaler offering triple therapy has been commercially available (although further triple therapy inhalers are expected onto the market shortly). Currently, patients with COPD receiving triple therapy must use at least two inhalers, typically a combined inhaled corticosteroid plus long-acting β_2-agonist in one inhaler and a long-acting muscarinic antagonist in another e.g. fluticasone/vilanterol plus umeclidinium, beclometasone / formoterol plus tiotropium.

Relevant NICE guidance:

Not reviewed by NICE

SMC – forthcoming submission

Disease Background

Chronic obstructive pulmonary disease (COPD) is a progressive disease, characterised by the presence of persistent respiratory symptoms, such as breathlessness, cough, and phlegm, and exacerbations. Much of the burden of COPD is due to exacerbations, which are associated with increased disease progression, reduced quality of life, and increased costs (especially from hospitalisation). Triple therapy with an inhaled corticosteroid, a long-acting β_2-agonist, and a long-acting muscarinic antagonist is recommended in patients with exacerbations despite initial treatment and is frequently used for the management of COPD.

In the UK, it is estimated that 3 million people have COPD, of whom 2 million are undiagnosed. Prevalence increases with age and most people are not diagnosed until they are in their 50s.[4] There are significant geographic variations in the prevalence of COPD, and it is closely associated with levels of deprivation. Unlike many other common chronic diseases, the prevalence of COPD has not declined in recent years.

Across the eight CCGs of Lancashire there are 38,504 patients on GP COPD registers, accounting for 2.4% of the total registered population, above the England prevalence of 1.9% (March 2017).[5]

Current treatment options

Currently, patients with COPD receiving triple therapy must use at least two inhalers, typically a combined inhaled corticosteroid plus long-acting β_2-agonist in one inhaler and a long-acting muscarinic antagonist in another e.g. fluticasone/vilanterol plus umeclidinium or beclometasone / formoterol plus tiotropium.

Summary of efficacy data in proposed use:

Pivotal studies

TRILOGY[6] was a randomised, parallel group, double-blind, active-controlled study done in 159 sites across 14 countries.

Summary - Eligible patients with COPD had post-bronchodilator forced expiratory volume in 1 s (FEV1) of lower than 50%, one or more moderate-to-severe COPD exacerbation in the previous 12 months, COPD Assessment Test total score of 10 or more, a Baseline Dyspnea Index focal score of 10 or less and a ratio of FEV1 to forced vital capacity (FVC) of less than 0·7. Patients also must have been using an inhaled corticosteroid plus a LABA, corticosteroid plus LAMA, or LABA plus a LAMA, or LAMA monotherapy for at least 2 months before screening (patients receiving triple therapy of an inhaled corticosteroid plus LABA and LAMA were not eligible).

Patients who met the inclusion and exclusion criteria at screening entered a 2-week open-label run-in period where they received beclometasone dipropionate (BDP) (100 µg) and formoterol fumarate (FF) (6 µg) in two actuations twice daily. Patients were then randomly assigned (1:1) to either continue BDP (100 µg) and FF (6 µg) or step-up to BDP (100 µg), FF (6 µg), and glycopyrronium bromide (GB) (12·5 µg) in two actuations twice daily for 52 weeks via pressurised metered-dose inhaler.

The three co-primary endpoints were pre-dose FEV1, 2-h post-dose FEV1, and Transition Dyspnea Index (TDI) focal score, all measured at week 26 in the intention-to-treat population (all patients who were randomly assigned and received at least one dose of study drug and had at least one post-baseline efficacy assessment). Safety outcomes were measured in the safety population (all patients who were randomly assigned and received at least one dose of study drug).

Secondary endpoints included moderate-to-severe COPD exacerbation rate over 52 weeks.

1368 patients received either BDP/FF/GB (n=687) or BDP/FF (n=681). At week 26, BDP/FF/GB improved pre-dose FEV1 by 0·081 L (95% CI 0·052–0·109; p<0·001) and 2-h post-dose FEV1 by 0·117 L (0·086–0·147; p<0·001) compared with BDP/FF. Mean TDI focal scores at week 26 were 1·71 for BDP/FF/GB and 1·50 for BDP/FF, with a difference of 0·21 (95% CI –0·08 to 0·51; p=0·160). Adjusted annual moderate-to-severe exacerbation frequencies were 0·41 for BDP/FF/GB and 0·53 for BDP/FF (rate ratio 0·77 [95% CI 0·65–0·92]; p=0·005), corresponding to a 23% reduction in exacerbations with BDP/FF/GB compared with BDP/FF.

Adverse events were reported by 368 (54%) patients with BDP/FF/GB and 379 (56%) with BDP/FF. One serious treatment-related adverse event occurred (atrial fibrillation) in a patient in the BDP/FF/GB group, but this event resolved in 15 days, and did not cause study drug discontinuation.

Results- BDP/FF/GB was superior to BDP/FF for both pre-dose FEV1 (adjusted mean difference 0·081 L [95% CI 0·052–0·109]; p<0·001) and 2-h post-dose FEV1 (adjusted mean difference 0·117 [0·086–0·147]; p<0·001) at week 26.

TDI focal score improved at week 26 in both groups; the mean difference between treatments (0·21 units [95% CI –0·08 to 0·51]) was not statistically significant.

Compared with BDP/FF, BDP/FF/GB showed significantly greater improvements in both pre-dose and 2-h post-dose FEV1 at all visits ,with a significantly higher proportion of patients responding to BDP/FF/GB than BDP/FF (defined as ≥100 mL increase in pre-dose FEV1) at weeks 26 and 52 .

The average pre-dose FEV1 mean difference between treatments over the duration of the study was 0·072 L (95% CI 0·048–0·096; p<0·001).

Increases in TDI focal score were observed in both groups at all visits, with a statistically significant difference between treatments favouring BDP/FF/GB at the two earliest visits (weeks 4 and 12). More than 50% of patients in each group reported clinically relevant improvements (≥1 unit) in TDI focal score at weeks 26 and 52; at week 26, patients were significantly more likely to respond to BDP/FF/GB than BDP/FF.

For SGRQ total score, clinically relevant improvements from baseline (decrease ≥4 units) occurred for the BDP/ FF/GB group at all visits from week 12 onwards, with statistically significant differences between the two groups at weeks 4, 12, and 52 (mean treatment difference at week 52 of –1·69 [95% CI –3·20 to –0·17]; p=0·029.

The use of rescue medication in puffs per day was significantly lower with BDP/FF/GB than with BDP/ FF up to week 26; patients in the BDP/FF/GB group had a significantly greater percentage of days with no rescue use than those in the BDP/FF group up to week 12.

The percentage of patients who had moderate-to severe exacerbations was lower with BDP/FF/GB (31%) than with BDP/FF (35%). The adjusted annual rate of moderate-to-severe exacerbations was 0·41 for the BDP/ FF/GB group and 0·53 for the BDP/FF group, with a rate ratio of 0·77 (95% CI 0·65–0·92; p=0·005), indicating a significant 23% reduction in the rate with BDP/FF/GB.

TRINITY[7] was a double-blind, parallel-group, randomised, controlled trial, at 224 sites across 15 countries. The study aimed to evaluate the use of extrafine BDP/FF/GB (fixed triple) over a monotherapy, tiotropium, with a free combination of BDP/FF in one inhaler and tiotropium in a second inhaler (open triple) as a control. Eligible patients had COPD, post-bronchodilator forced expiratory volume in 1 s (FEV1) of less than 50%, at least one moderate-to-severe COPD exacerbation in the previous 12 months, and a COPD Assessment Test total score of at least 10.

Summary - Patients were randomised (2:2:1) to 52 weeks treatment with tiotropium, fixed triple, or open triple. The primary endpoint was moderate-to-severe COPD exacerbation rate. The key secondary endpoint was change from baseline in pre-dose FEV1 at week 52.

2691 patients received fixed triple (n=1078), tiotropium (n=1075), or open triple (n=538). Moderate-to-severe exacerbation rates were 0·46 (95% CI 0·41–0·51) for fixed triple, 0·57 (0·52–0·63) for tiotropium, and 0·45 (0·39–0·52) for open triple; fixed triple was superior to tiotropium (rate ratio 0·80 [95% CI 0·69–0·92]; p=0·0025). For week 52 pre-dose FEV1, fixed triple was superior to tiotropium (mean difference 0·061 L [0·037 to 0·086]; p<0·0001) and non-inferior to open triple (–0·003L [–0·033 to 0·027]; p=0·85).

Adverse events were reported by 594 (55%) patients with fixed triple, 622 (58%) with tiotropium, and 309 (58%) with open triple.

Study detail - Patients who met the inclusion and exclusion criteria at a screening visit (visit 1) entered a 2-week open-label run in period, during which they received tiotropium 18 µg, one inhalation per day (in the morning) via single-dose dry-powder inhaler. At the end of the 2-week run-in (visit 2), patients were randomised with a 2:2:1 ratio to one of three treatment groups.

Eligible patients were 40 years of age or older; current or ex-smokers; had a diagnosis of COPD, with post-bronchodilator (salbutamol 400 µg) forced expiratory volume in 1 s (FEV1) of less than 50% and a ratio of FEV1 to forced vital capacity of less than 0·7; had at least one moderate or severe COPD exacerbation in the previous 12 months; and used an inhaled corticosteroid plus long-acting β_2-agonist (as an open or fixed combination), or inhaled corticosteroid plus long-acting muscarinic antagonist, or inhaled long-acting β_2-agonist plus long-acting muscarinic antagonist (as an open or fixed combination), or long-acting muscarinic antagonist monotherapy for at least 2 months before screening - patients receiving triple therapy of inhaled corticosteroid, long-acting β_2-agonist and long-acting muscarinic antagonist were not eligible.

Primary objective was to assess efficacy of the fixed triple dose versus tiotropium in terms of moderate to severe COPD exacerbation rate for 52 weeks of treatment. The two key secondary objectives were both based on change from baseline in pre-dose FEV1 at week 52 - to assess efficacy of fixed triple versus tiotropium with a superiority analysis, and to assess fixed triple therapy versus open triple therapy with a non-inferiority analysis. The secondary efficacy variables were time to first moderate to severe COPD exacerbation, and to first severe COPD exacerbation; rate of severe and of moderate COPD exacerbations throughout 52 weeks of treatment; pre-dose FEV1 at all other clinic visits and the mean over the treatment period; FEV1 response (change from baseline in pre-dose FEV1 ≥100 mL) at weeks 26 and 52; pre-dose inspiratory capacity at all clinic visits; SGRQ response at weeks 26 and 52; SGRQ total score at all clinic visits; and percentage of days without rescue medication use and average number of puffs per day.

Results - 2691 patients were randomly assigned to one of the treatment groups, with 986 (91%) of 1078 completing the study in the fixed triple group, 914 (85%) of 1075 in the tiotropium group, and 496 (92%) of 538 in the open triple group. Patients in the tiotropium group were more likely to prematurely withdraw from the study than either of the other two groups (p<0·0001).

The rates of moderate-to-severe COPD exacerbations were 0·46 per patient per year for fixed triple, 0·57 for tiotropium, and 0·45 for open triple. Extrafine fixed triple was superior to tiotropium, with an adjusted rate ratio (RR) of 0·80 (95% CI 0·69–0·92; p=0·0025; the rates of moderate-to-severe exacerbations were similar with fixed triple and open triple.

The time to first severe exacerbation was prolonged with fixed triple compared with tiotropium (HR 0·70 [95% CI 0·52–0·95]; p=0·0208), and was similar for fixed triple and open triple (1·05 [0·70–1·56]; p=0·82).

The adjusted mean changes from baseline in pre-dose FEV1 at week 52 (the key secondary efficacy variable) were 0·082 L (95% CI 0·065 to 0·100) for fixed triple, 0·021 L (0·003 to 0·039) for tiotropium and 0·085 L (0·061 to 0·110) for open triple. Both of the key secondary objectives were met, with fixed triple superior to tiotropium (adjusted mean difference 0·061 L [95% CI 0·037 to 0·086]; p<0·0001) and non-inferior to open triple (–0·003 L [–0·033 to 0·027]; p=0·85) in pre-dose FEV1 at week 52.

Compared with patients receiving fixed triple, those receiving tiotropium required more rescue medication, both when analysed in terms of puffs per day and the percentage of days with no use, with rescue medication use similar in the fixed triple and open triple groups.

Overall conclusions on clinical efficacy

TRILOGY shows that in patients with COPD who have severe or very severe airflow limitation, symptoms, and an exacerbation history, triple therapy with BDP/FF/GB had a greater effect on pre-dose and 2-h post-dose FEV1 than BDP/FF. For the co-primary endpoint measuring breathlessness (TDI), superiority of BDP/FF/GB over BDP/FF was not shown. The rate of moderate-to-severe COPD exacerbations was 23% lower with BDP/FF/GB compared with BDP/FF, with the time to first exacerbation significantly longer with triple therapy. Thus, the greater improvement in lung function with BDP/FF/GB compared with BDP/FF was more clearly accompanied by a reduction in exacerbations than an improvement in breathlessness in this group of patients. Furthermore, BDP/FF/GB had a greater effect on health related quality of life than BDP/FF.

TRINITY met the primary and both key secondary endpoints. Extrafine fixed triple resulted in a 20% (95% CI 8–31) reduction in the rate of moderate-to-severe COPD exacerbations compared with tiotropium, together with a 0·061 L mean improvement in pre-dose FEV1. Furthermore, the non-inferiority of fixed triple relative to open triple was shown for pre-dose FEV1. Fixed triple reduced both moderate and severe exacerbation rates, hyperinflation (as measured by inspiratory capacity), and rescue medication use, with more SGRQ responders compared with tiotropium, and effects generally similar to open triple.

Summary of safety data:

Treatment-emergent adverse events were captured throughout the studies, with all events judged by the investigator as having reasonable causal association to a medical product considered to be treatment-related adverse events.

TRILOGY - A similar proportion of patients had treatment emergent adverse events in the two groups.

Most events were mild or moderate in severity. One treatment-related serious adverse event occurred (atrial fibrillation) in a patient in the BDP/FF/GB group, and this event resolved in 15 days, and did not cause study drug discontinuation. Treatment-emergent adverse events resulted in death in a similar percentage of patients in the two groups. None of the deaths were assessed to be related to the study treatment. Mean changes from baseline in blood pressure, heart rate, and QTc interval were small and similar in the two groups. The percentages of abnormal QTc interval absolute values and changes were similar in both treatment groups. In the subgroup of patients with Holter assessments, changes from baseline in 24 h average heart rate to weeks 26 and 52 were minimum and similar in both groups.

TRINITY - A similar proportion of patients had adverse events in the three groups . Most events were mild or moderate in severity. Pneumonia was reported in a small number of patients, with similar incidence in the three treatment groups. One serious adverse event occurred in one patient in the tiotropium group; the patient experienced an episode of angina pectoris, considered moderate in severity, and although the patient fully recovered it resulted in withdrawal from the study.

Fewer patients experienced adverse events leading to discontinuation of study drug in the two triple therapy groups than did in the tiotropium group. The most common adverse event leading to study drug discontinuation was COPD exacerbation (eight [1%] patients in the fixed triple group, 14 [1%] in the tiotropium group, and 5 [1%] in the open triple group). Adverse events resulted in 57 deaths. None of the deaths was considered related to study treatment.

The Summary of product characteristics states that the most frequently reported adverse reactions with Trimbow were oral candidiasis (which occurred in 0.5% of the exposed subjects), which is normally associated with inhaled corticosteroids; muscle spasms (0.5%), which can be attributed to the long-acting beta$_2$-agonist component; dry mouth (0.5%), which is a typical anticholinergic effect. The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from available data).

Adverse events

MedDRA system organ class	Adverse reaction	Frequency
Infections and Infestations	Pneumonia (in COPD patients)[a], pharyngitis[a], oral candidiasis, urinary tract infection[a], nasopharyngitis[a] Influenza[a], oral fungal infection, oropharyngeal candidiasis, oesophageal candidiasis[a], sinusitis[a], rhinitis[a], gastroenteritis[a], vulvovaginal candidiasis[a] Lower respiratory tract infection (fungal)	Common Uncommon Rare
Blood and lymphatic system disorders	Granulocytopenia[a] Thrombocytopenia[a]	Uncommon Very Rare
Immune system disorders	Dermatitis allergic[a] Hypersensitivity reactions, including erythema, lips, face, eye and pharyngeal oedema	Uncommon Rare
Endocrine disorders	Adrenal suppression[a]	Very Rare
Metabolism and nutrition disorders	Hypokalaemia[a], hyperglycaemia[a] Decreased appetite	Uncommon Rare

Psychiatric disorders	Restlessness[a] Psychomotor hyperactivity[a], sleep disorders[a], anxiety[a], depression[a], aggression[a], behavioural changes (predominantly in children) [a] Insomnia	Uncommon Frequency not known Rare
Nervous system disorders	Headache Tremor[a], dizziness[a], dysgeusia[a], hypoaesthesia[a] Hypersomnia	Common Uncommon Rare
Eye disorders	Glaucoma[a], cataract[a]	Very Rare
Ear and labyrinth disorders	Otosalpingitis[a]	Uncommon
Cardiac disorders	Atrial fibrillation, electrocardiogram QT prolonged, tachycardia, tachyarrhythmia[a], palpitations Angina pectoris (stable[a] and unstable), ventricular extrasystoles[a], nodal rhythm, sinus bradycardia	Uncommon Rare
Vascular disorders	Hyperaemia[a], flushing[a] Extravasation blood, hypertension	Uncommon Rare
Respiratory, thoracic and mediastinal disorders	Dysphonia Cough, productive cough[a], throat irritation, epistaxis[a] Bronchospasm paradoxical[a], oropharyngeal pain Dyspnoea[a]	Common Uncommon Rare Very Rare
Gastrointestinal disorders	Diarrhoea[a], dry mouth, dysphagia[a], nausea[a], dyspepsia[a], burning sensation of the lips[a], dental caries[a]	Uncommon
Skin and subcutaneous tissue disorders	Rash[a], urticaria[a], pruritus[a], hyperhidrosis[a] Angioedema[a]	Uncommon Rare
Musculoskeletal and connective tissue disorders	Muscle spasms, myalgia, pain in extremity[a], musculoskeletal chest pain[a] Growth retardation[a]	Uncommon Very Rare
Renal and urinary disorders	Dysuria[a], urinary retention[a] Nephritis[a]	Uncommon Rare
General disorders and administration site conditions	Fatigue[a], asthenia[a] Oedema peripheral[a]	Uncommon Very Rare
Investigations	C-reactive protein increased[a], platelet count increased[a], free fatty acids increased[a], blood insulin increased[a], blood ketone body increased[a], blood cortisol decreased[a] Blood pressure increased[a], blood pressure decreased[a] Bone density decreased[a]	Uncommon Rare Very Rare

[a] Adverse reactions reported in the SPC of at least one of the individual components, but not observed as adverse reactions in the clinical development of Trimbow

Strengths and limitations of the evidence:

Strengths:

- Both studies were double-blind, parallel-group, randomised, controlled trials, with large patient numbers.
- Both studies were carried out over a period of 52 weeks

Limitations:

- **TRILOGY** - inhaled corticosteroid and long-acting β_2-agonist treatment was the comparator group, GOLD 2017 now recommends use of LABA +LAMA in preference to LABA +ICS for the treatment of COPD patients. Therefore, most COPD patients will progress to triple therapy from LABA + LAMA, so comparator arm bears little relevance to current clinical practice / recommendations. This was acknowledged by the study authors “Our study did not address

the benefit of escalation to triple therapy from a long-acting β_2-agonist/long-acting muscarinic antagonist combination. This is an important point to examine in the future, especially given that a study[8] suggested that long-acting β_2-agonist/long-acting muscarinic antagonist treatment is more effective on a wide range of endpoints including exacerbations than an inhaled corticosteroid/long-acting β_2-agonist combination."

- The 23% reduction in the exacerbation rate, which is above the suggested minimum clinically important difference, can be attributed to the long-acting muscarinic antagonist component of BDP/FF/GB.
- A Cochrane review[9] recently concluded that for the treatment of COPD, LAMA+LABA has fewer exacerbations, a larger improvement of FEV1, a lower risk of pneumonia, and more frequent improvement in quality of life as measured by an increase over 4 units or more of the SGRQ. These data were supported by low or moderate quality evidence generated from mainly participants with moderate to severe COPD in heterogeneous trials with an observation period of less than one year- findings support the recently updated GOLD guidance.
- Patients already on triple therapy (as two separate inhalers) were excluded from the study and so no direct comparison can be made.
- **TRINITY** – does not answer the question of the value of adding an inhaled corticosteroid to a long-acting β_2-agonist plus long-acting muscarinic antagonist combination, even though this is now the recommended treatment option.
- Patients being treated as per GOLD 2017 guidelines would not progress from treatment with a long acting muscarinic antagonist (tiotropium) to triple therapy, but instead would progress to treatment with a long-acting β_2-agonist/long-acting muscarinic antagonist combination.
- Patients received tiotropium (LAMA) for run in period (irrespective of their current treatment – majority of patients on dual therapy pre study and therefore this represents a step down in treatment), but were then escalated to treatment with triple therapy – this would not happen in current clinical practice.
- Majority of study patients were on ICS /LABA therapy at study entry which is not representative of the currently recommended clinical treatment pathway.
- The fixed triple therapy provided similar results to the open triple therapy.
- Lower than expected exacerbation rates were observed in all three groups.
- Patients already on triple therapy (as two separate inhalers) were excluded from the study and so no direct comparison can be made.

Prescribing and risk management issues:

The licence for Trimbow is for maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta$_2$-agonist. However, the majority of patients requiring a step up to triple therapy will not currently be being treated with an ICS / LABA combination and as such there is the potential for Trimbow to be used outside of its licence.

The current recommendation from the Global Initiative for Chronic Obstructive Lung Disease strategy document[3] (GOLD) for primary choice of a dual therapy; and their preferred route before to escalation to triple therapy is a LABA /LAMA combination, citing that a LABA / LAMA combination was superior to a LABA / ICS combination in preventing exacerbations and other patient reported outcomes.[3,8]

Commissioning considerations:

Anticipated patient numbers and net budget impact

Across the eight clinical commissioning groups of Lancashire, there are 38,504 patients on GP COPD registers, accounting for 2.4% of the total registered population, above the England

prevalence of 1.9%.[10] The proportion of COPD patients treated with triple therapy has been estimated to be between 23%[11] and 25.5%[12], equating to 8,855 - 9,819 patients across Lancashire. However, one of the studies[11] found that nearly a quarter of the patients' prescribed triple therapy at baseline stepped down treatment within 24 months.

If 9,000 patients across Lancashire were to be treated with Trimbow this would incur an annual cost of £44.50 x 12 x 9000 = £4,806,000.

The current 1st line LMMG recommended triple therapy[13] (Symbicort 400/12 + Spiriva Respimat) for 9000 patients has an annual cost of £61.00 (£ 38.00 + 23.00) x 12 x 9000 = £6,588,000

The proposed Ellipta treatment pathway triple therapy for 9000 patients has an annual cost of £49.50 (£27.50 + 22.00) x 12 x 9000 = £5,346,000. However, an Ellipta triple therapy device is expected on the market shortly (Q4 2017) and this cost may be reduced. It would also provide device continuity within a pathway if an ICS/LABA/LAMA is required.

Associated additional costs or available discounts:

At a cost of £44.50 for 30 days treatment, Trimbow represents a cost saving compared with the open triple therapies currently recommended in the LMMG COPD pathway. However, it is comparable in price to the open triple therapy in the proposed Ellipta COPD treatment pathway (a fixed triple therapy in the Ellipta device is also expected to be available Q4 2017).

Consideration should also be paid to the prescribing and risk management issues raised above i.e. potential use outside of licence and also that, in GOLD 2017, triple therapy is the preferred treatment only for those patients in Group D with persistent symptoms and further exacerbations and as such, in the future the number of patients for whom triple therapy is appropriate should be reduced.

Productivity, service delivery, implementation:

As a MDI device, Trimbow would not fit into the proposed LMMG COPD device driven pathways, but would introduce yet another device for the patients to become familiar with and educated on the use of.

There is also a risk for use outside of licence.

Innovation, need, equity:

Trimbow provides fixed triple therapy in one inhaler device.

However, superior clinical efficacy has not been demonstrated when compared to open triple therapy (two separate inhalers).

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: high quality randomised controlled trials (RCTs) with low risk of bias systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: clinical trials at moderate or high risk of bias systematic reviews or meta-analyses of such clinical trials or with inconsistent findings cohort studies case-control studies	
Level 3	Disease-oriented evidence, or evidence from: consensus guidelines expert opinion case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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References

[1] Summary of Product Characteristics Trimbow 87 micrograms/5 micrograms/9 micrograms pressurised inhalation, solution. Last Updated on eMC 26-Jul-2017 https://www.medicines.org.uk/emc/medicine/33828 (Accessed online 27th July 2017)

[2] Wurst KE, Punekar YS, Shukla A. Treatment evolution after COPD diagnosis in the UK primary care setting. PLoS One 2014;9:e105296.

[3] Global Initiative for Chronic Obstructive Lung Disease global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease 2017 report

[4] Chronic obstructive pulmonary disease in adults. NICE Quality standard Published: 28 July 2011 nice.org.uk/guidance/qs10 (last updated February 2016)

[5] http://www.lancashire.gov.uk/lancashire-insight/health-and-care/long-term-conditions/respiratory-disease.aspx (accessed online 18th July 2017)

[6] Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. Singh D et al; The Lancet, Vol 388 September 3, 2016; 963 - 973

[7] 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. Vestbo J et al; www.thelancet.com Published online April 3, 2017 http://dx.doi.org/10.1016/S0140-6736(17)30188-5

[8] Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. N Engl J Med 2016; 374: 2222–34.

[9] Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD) Horita N et al; Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD012066. DOI: 10.1002/14651858.CD012066.pub2.

[10] Lancashire County Council – Respiratory Disease http://www.lancashire.gov.uk/lancashire-insight/health-and-care/long-term-conditions/respiratory-disease.aspx (accessed online July 2017)

[11] Treatment Evolution after COPD Diagnosis in the UK Primary Care Setting: Wurst K E et al; PLoS ONE 9(9): e105296. https://doi.org/10.1371/journal.pone.0105296 http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0105296 (accessed online July 2017)

[12] Initiation of triple therapy maintenance treatment among patients with COPD in the US: Simeone J C et al; Int J Chron Obstruct Pulmon Dis. 2017; 12: 73–83 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5191839/ (accessed online July 2017)

[13] LMMG COPD Desktop Guidelines March 2014 (currently under review) http://www.lancsmmg.nhs.uk/download/guidelines/COPD%20desktop%20guide%20(Version%201.4).pdf (accessed online July 2017)