New Medicine Recommendation
Trelegy Ellipta▼

(92 micrograms fluticasone furoate /55 micrograms umeclidinium /22 micrograms vilanterol) inhalation powder, pre-dispensed, as a 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 β2-agonist

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
- Trelegy fits into the Ellipta strategy pathway of the LMMG COPD guideline and could replace the current third step which involves use of both Incruse Ellipta and Relvar Ellipta
- There may be other groups of patients who are established on LABA/ICS inhalers who could benefit from Trelegy should their condition require a LAMA component, with the added convenience of a single inhaler providing all three drug components.
- Trelegy costs less than the equivalent combination of currently available inhalers when used to provide an equivalent regimen of LAMA/LABA/ICS.

Summary of supporting evidence

The efficacy of Trelegy Ellipta (92/55/22 micrograms) administered as a once daily treatment in patients with a clinical diagnosis of COPD has been evaluated in one 24-week active-controlled study with an extension up to 52 weeks in a subset of subjects (FULFILTrial)[1]. Patients were required to be symptomatic with a CAT score ≥10 and on COPD maintenance therapy for at least three months prior to study entry. The mean age was 63.9 years, with 50% of patients aged 65 or over. At screening, the mean post bronchodilator FEV1 was 45% of predicted and 65% of patients reported a history of moderate/severe exacerbation in the past year. At study entry, the most common COPD medication combinations reported were ICS +LABA+LAMA (28%), ICS+LABA (29%), LAMA+LABA (10%) and LAMA (9%). These patients may have also been taking other COPD medications (e.g. mucolytics or leukotriene receptor antagonists).

Trelegy Ellipta (92/55/22 micrograms) administered once daily demonstrated a statistically significant improvement in lung function (as defined by change from baseline trough FEV1 at Week 24; co-primary endpoint) compared with budesonide/formoterol (BUD/FOR) 400 /12 micrograms administered twice-daily. Bronchodilatory effects with Trelegy Ellipta were evident on the first day of treatment and were maintained over the 24 week treatment period (changes from baseline in FEV1 were 90-222 mL on Day 1 and 160-339 mL at Week 24).

Trelegy Ellipta demonstrated a statistically significant improvement compared to BUD/FOR at Week 24 for Health Related Quality of Life (HRQoL) measured by the St George's Respiratory Questionnaire (SGRQ) total score (co-primary endpoint), SGRQ responder analysis, COPD Assessment Test (CAT) score, CAT responder analysis, respiratory symptoms measured using the Evaluating Respiratory Symptoms in COPD (E-RS:COPD) and sub-scale scores over Weeks 21-24, breathlessness measured using the Transitional Dyspnoea Index (TDI) focal score at Week 24, and

rescue medication use measured by mean number of occasions of rescue medication use per day over Weeks 1-24.

Trelegy Ellipta demonstrated a statistically significant reduction in the annual rate of moderate/severe exacerbations (i.e. requiring treatment with antibiotics or corticosteroids or hospitalisation; extrapolated from data up to Week 24) compared with BUD/FOR. A reduction in the risk of a moderate/severe exacerbation (i.e. requiring treatment with antibiotics or corticosteroids or hospitalisation) was observed with Trelegy Ellipta compared with BUD/FOR (based on analysis of the time to first exacerbation).

InforMing the PAthway of COPD Treatment (IMPACT)[2] study was a randomised, double-blind, 52-week study that compared the efficacy and safety of fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) 100/62.5/25 mcg with FF/VI 100/25 mcg and UMEC/VI 62.5/25 mcg in symptomatic patients with COPD and a history of exacerbations.

FF/UMEC/VI significantly reduced the annual rate of moderate or severe exacerbations compared to FF/VI (0.91 vs. 1.07/year; 15% reduction) and UMEC/VI (0.91 vs. 1.21/year; 25% reduction) (P <0.001 for both comparisons).

The change from baseline in trough forced expiratory volume in 1 second (FEV1) for FF/UMEC/VI compared with FF/VI was 97 mL and compared with UMEC/VI was 54 mL (P < 0.001 for both comparisons).

The change from baseline in St. George's Respiratory Questionnaire (SGRQ) for FF/UMEC/VI compared with FF/VI was -1.8 units and compared with UMEC/VI was -1.8 units (P < 0.001 for both comparisons).

An analysis of time to first on-treatment moderate or severe COPD exacerbation demonstrated a 14.8% reduction in risk for FF/UMEC/VI compared with FF/VI and a 16.0% reduction in risk compared with UMEC/VI (P < 0.001 for both comparisons).

Based on the positive results of the landmark 10,355-patient IMPACT study, the manufacturers have also announced the filing (November 2017) of a supplemental New Drug Application (sNDA) with the US Food and Drug Administration (FDA) for the use of Trelegy Ellipta for an expanded indication for the maintenance treatment of airflow obstruction and reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD).

Details of Review

Name of medicine (generic & brand name): 92 micrograms fluticasone furoate /55 micrograms umeclidinium /22 micrograms vilanterol, Trelegy Ellipta

Strengths and forms:

Trelegy Ellipta 92 micrograms/55 micrograms/22 micrograms inhalation powder, pre-dispensed. White powder in a light grey inhaler (Ellipta) with a beige mouthpiece cover and a dose counter.

Dose and administration:

The recommended and maximum dose is one inhalation of Trelegy Ellipta 92/55/22 micrograms once daily, at the same time each day

BNF therapeutic class / mode of action: Chapter 3, Respiratory system, Airways disease, obstructive

Fluticasone furoate/umeclidinium/vilanterol is a combination of inhaled synthetic corticosteroid, long-acting muscarinic receptor antagonist and long-acting beta2-adrenergic agonist (ICS/LAMA/LABA).

Following oral inhalation, umeclidinium and vilanterol act locally on airways to produce bronchodilation by separate mechanisms and fluticasone furoate reduces inflammation.

Fluticasone furoate is a corticosteroid with potent anti-inflammatory activity. The precise mechanism through which fluticasone furoate affects COPD symptoms is not known. Corticosteroids have been shown to have a wide range of actions on multiple cell types

(e.g. eosinophils, macrophages, lymphocytes) and mediators (e.g. cytokines and chemokines) involved in inflammation.

Umeclidinium is a long-acting muscarinic receptor antagonist (also referred to as an anticholinergic). Umeclidinium exerts its bronchodilatory activity by competitively inhibiting the binding of acetylcholine with muscarinic receptors on airway smooth muscle. It demonstrates slow reversibility at the human M3 muscarinic receptor subtype in vitro and a long duration of action in vivo when administered directly to the lungs in pre-clinical models.

Vilanterol is a selective long-acting, beta2-adrenergic receptor agonist (LABA). The pharmacologic effects of beta2-adrenergic agonists, including vilanterol, are at least in part attributable to stimulation of intracellular adenylate cyclase, the enzyme that catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Licensed indication(s): [3]

Trelegy Ellipta is indicated as a 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 β2-agonist

Proposed use:

Within licensed indication

Course and cost:

Ongoing maintenance treatment.

NHS list price is £44.50 per 30 actuation device (equates to 30 days treatment)

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 β2-agonist (LABA) or ICS plus long-acting muscarinic antagonist (LAMA) progressed to triple therapy. [4]

Trimbow[5] is another 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) which has recently been marketed for the same indication at a cost of £44.50 per 120 actuation device (30 days treatment at a recommended dose of two inhalations twice a day).

The components of Trelegy Ellipta are also available as two separate inhalers Incruse Ellipta (umeclidinium) plus Relvar Ellipta (fluticasone + vilanterol) with a combined cost of £49.50, which are currently included in the LMMG COPD Treatment Guidelines.

The Global Initiative for Chronic Obstructive Lung Disease strategy document[6] recommends inhaled triple pharmacologic therapy (ICS/LAMA/LABA) only for patients with advanced COPD with

persistent symptoms and risk of exacerbations and this is reflected in the LMMG COPD Treatment Guidelines.

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.[7]

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).[8]

Current treatment options

Currently, patients with COPD receiving triple therapy must use **either** 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 **or** the recently available triple therapy combination inhaler (Trimbow) which is used twice daily.

Summary of efficacy data in proposed use:

NCT01957163; NCT02119286[9]

Two early 12-week, double-blind, placebo-controlled, parallel-group, multicenter studies were carried out with the objective of evaluating the efficacy and safety of umeclidinium (UMEC 62.5 mg and 125 mg) added to fluticasone furoate/vilanterol (FF/VI, 100/25 mg) in chronic obstructive pulmonary disease (COPD).

Eligible patients were randomized 1:1:1 to treatment with once-daily blinded UMEC 62.5 mg , UMEC 125 mg or placebo (PBO) added to open-label FF/VI (delivering 92/22 mg; N = 1238 [intent-to-treat population]). The primary endpoint was trough forced expiratory volume in one second (FEV1) on Day 85; the secondary endpoint was 0-6 h post-dose weighted mean (WM) FEV1 at Day 84. Health-related quality of life was reported using St George's respiratory questionnaire (SGRQ). Adverse events (AEs) were also assessed.

In both studies, trough FEV1 was significantly improved with UMEC+ FF/VI (62.5 mg and 125 mg) versus PBO + FF/VI (range: 0.111- 0.128 L, all $p < 0.001$ [Day 85]), as was 0- 6 h post-dose WM FEV1 (range: 0.135-0.153 L, all $p < 0.001$ [Day 84]). SGRQ results were inconsistent, with statistically significant improvements with UMEC + FF/VI versus PBO + FF/VI in one study only and with UMEC 62.5 mg only (difference in SGRQ total score from baseline between treatments: -2.16, $p < 0.05$). Across all treatment groups, the overall incidences of AEs were similar (30-39%), as were cardiovascular AEs of special interest (<1-3%) and pneumonia AEs (0-1%).

FULFIL Trial[1]

The primary objective of this trial was to compare the effects of once-daily triple therapy on lung function and health-related quality of life with twice-daily ICS/LABA therapy.

FULFIL was a phase III, randomized, double-blind, double-dummy, parallel-group, multicentre study comparing 24 weeks of once-daily triple therapy (fluticasone furoate/ umeclidinium/ vilanterol 100 µg/62.5 µg/25 µg; ELLIPTA® inhaler) with twice-daily ICS/LABA therapy (budesonide/formoterol 400 µg/12 µg; Symbicort Turbohaler®).

Patients were randomised to receive once daily FF/UMEC/VI (100 µg/62.5 µg/25 µg) using a single ELLIPTA® inhaler and twice-daily placebo using the Turbohaler®, or twice-daily budesonide/formoterol (BUD/FOR) (400 µg/12 µg) using the Turbohaler® and once-daily placebo using the ELLIPTA® inhaler. All patients took one inhalation from the ELLIPTA® inhaler in the morning and two inhalations (one in the morning and one in the evening) from the Turbohaler® to minimize the impact of different dosing regimens.

There was a 2-week run-in period, during which medications at screening were unchanged, followed by a 24-week treatment period. A subset of the first 430 patients to enrol in the trial and consent to longer-term treatment remained on blinded study treatment for up to 52 weeks. Co-primary endpoints were change from baseline in trough forced expiratory volume in 1 second (FEV1) and in St George's Respiratory Questionnaire (SGRQ) Total score, at Week 24.

Efficacy and safety endpoints were analysed up to Week 24 in the intent-to-treat (ITT) population and up to Week 52 in the extension (EXT) population.

FULFIL enrolled patients with COPD aged ≥ 40 years defined as Global Initiative for Chronic Obstructive Lung Disease Group D: FEV1 < 50% and COPD Assessment Test ≥ 10, or patients with FEV1 ≥ 50–< 80% and COPD Assessment Test ≥ 10, and either ≥ 2 moderate exacerbations or ≥ 1 severe exacerbation in the past year. Patients were required to be receiving daily maintenance therapy for COPD for ≥ 3 months.

Spirometry was performed in all patients at baseline and at Weeks 2, 4, 12, 24, and at Weeks 36 and 52 in the EXT population. A moderate exacerbation was defined as having worsening symptoms of COPD that required treatment with oral/systemic corticosteroids and/or antibiotics. A severe exacerbation was defined as worsening symptoms of COPD that required treatment with in-patient hospitalisation.

In the intent-to-treat population (N = 1,810) at Week 24 for triple therapy (n = 911) and ICS/LABA therapy (n = 899): mean change from baseline in FEV1 was 142 mL (95% confidence interval [CI], 126,158) and -29 mL (95% CI, -46, -13), respectively; mean change from baseline SGRQ was -6.6 units (95% CI, -7.4,-5.7) and -4.3 units (95% CI, -5.2,-3.4), respectively. For both endpoints, the between-group differences were statistically significant ($P < 0.001$). Similar findings in change from baseline in trough FEV1 were observed in the EXT population at Week 52. The mean change from baseline in trough FEV1 was 126 mL (95% CI, 92,159) for FF/UMEC/VI and -53 mL (95% CI, - 87,-20) for BUD/FOR. The mean change from baseline in SGRQ Total score in the EXT population was -4.6 units (95% CI, -6.5,-2.6) with FF/UMEC/VI and -1.9 units (95% CI, -3.9,0.1) with BUD/FOR, and although the between-treatment difference was of a similar magnitude to that observed in the ITT population, it did not reach statistical significance.

It was also found that in the ITT population at Week 24, an increase of ≥ 100 mL from baseline in trough FEV1 was achieved by a larger proportion of patients in the FF/UMEC/VI group (453;50%) than in the BUD/FOR group (184; 21%).

There was a statistically significant reduction in moderate/severe exacerbation rate with triple versus ICS/LABA therapy (35% reduction, 95% CI, 14,51; P = 0.002). The safety profile of triple therapy reflected the known profiles of the components.

IMPACT Trial [2,10](results not yet published)

The InforMing the PAthway of COPD Treatment (IMPACT) study was designed to evaluate the efficacy and safety of fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) versus FF/VI or UMEC/VI over a 52-week treatment period.

This is a phase III, randomised, double-blind, three-arm, parallel-group, global multicentre study comparing the rate of moderate and severe exacerbations between FF/UMEC/VI and FF/VI or UMEC/VI over a 52-week treatment period. The study recruited 10,355 patients from approximately 1070 centres. Eligible patients are aged ⩾40 years, with symptomatic advanced COPD (Global initiative for chronic Obstructive Lung Disease (GOLD) group D) and an exacerbation in the previous 12 months. This is a superiority study, which is designed to show the benefit of FF/UMEC/VI over FF/VI and UMEC/VI.

A number of secondary endpoints were assessed e.g. changes in QoL, lung function and the relative magnitude of benefit of the three therapies on exacerbation prevention by baseline blood eosinophil count.

Throughout the study, each COPD exacerbation was categorised based on severity, as mild, moderate or severe (Mild = Worsening symptoms of COPD that are self-managed by the patient. Mild exacerbations are not associated with the use of corticosteroids or antibiotics. Moderate= Worsening symptoms of COPD that require treatment with oral/systemic corticosteroids and/or antibiotics. Severe = Worsening symptoms of COPD that require treatment with in-patient hospitalisation). Blood samples for eosinophil counts will be taken at the screening visit and at the randomisation visit. This will provide two baseline values, 2 weeks apart, to allow assessment of stability. Further blood samples for eosinophil counts will be taken at weeks 16, 28 and 52, or when the investigational product is discontinued.

The study consisted of a 2-week run-in period, a 52-week treatment phase and a 1-week safety follow-up phase. Patients were randomised 2:2:1 to one of three treatment groups: FF/UMEC/VI 100/62.5/25 µg, FF/VI 100/25 µg or UMEC/VI 62.5/25 µg, respectively, delivered via an identical ELLIPTA dry powder inhaler.

Although not yet published the available headline results show that FF/UMEC/VI significantly reduced the annual rate of moderate or severe exacerbations compared to FF/VI (0.91 vs. 1.07/year; 15% reduction) and UMEC/VI (0.91 vs. 1.21/year; 25% reduction) ($P < 0.001$ for both comparisons). The change from baseline in trough forced expiratory volume in 1 second (FEV1) for FF/UMEC/VI compared with FF/VI was 97 mL and compared with UMEC/VI was 54 mL ($P < 0.001$ for both comparisons). The change from baseline in St. George's Respiratory Questionnaire (SGRQ) for FF/UMEC/VI compared with FF/VI was -1.8 units and compared with UMEC/VI was -1.8 units ($P < 0.001$ for both comparisons). An analysis of time to first on-treatment moderate or severe COPD exacerbation demonstrated a 14.8% reduction in risk for FF/UMEC/VI compared with FF/VI and a 16.0% reduction in risk compared with UMEC/VI ($P < 0.001$ for both comparisons).

Based on the positive results of the IMPACT study, the manufacturers have also announced the filing (November 2017) of a supplemental New Drug Application (sNDA) with the US Food and Drug Administration (FDA) for the use of Trelegy Ellipta for an expanded indication for the maintenance treatment of airflow obstruction and reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD). This is expected to be replicated with the EMA.

Overall conclusions on the clinical efficacy

The **FULFIL** trial demonstrated that once-daily FF/UMEC/VI offered clinically meaningful and statistically significant improvements at Week 24 in lung function and health-related quality of life compared with BUD/FOR. At each 4-weekly time point, FF/UMEC/VI demonstrated greater symptom reduction than BUD/FOR.

Clinically meaningful and statistically significant reductions in exacerbation rates for patients with COPD were also observed with FF/UMEC/VI compared with BUD/FOR, at Week 24. The benefits of FF/UMEC/VI on lung function, health-related quality of life, and exacerbation rate were sustained over 52 weeks in the EXT population.

The magnitude of the between-treatment difference in SGRQ Total score between treatment groups at Week 52 failed to achieve statistical significance, possibly due to the smaller size of this subgroup.

The lung function findings reported here are in keeping with the results of shorter studies of triple therapy using FF/VI and UMEC in two separate inhalers[9].

FULFIL was designed to be as inclusive as possible, allowing patients with COPD who also had significant cardiovascular disease to be enrolled. Furthermore, patients remained on their usual standard medications during the run-in and were not artificially required to withdraw medications. This meant the study population may more closely reflect the real-world population of patients with COPD.

The **IMPACT** Trial would appear to demonstrate significant reduction in the annual rate of moderate or severe exacerbations for FF/UMEC/VI compared to both FF/VI and UMEC/VI, as well as a significant change from baseline in FEV_1, and SGRQ. There was also a significant reduction in risk for FF/UMEC/VI compared with FF/VI and UMEC /VI when analysing the time to first on-treatment moderate or severe COPD exacerbation.

Summary of safety data

FULFIL Trial[1]

The incidence of on-treatment AEs in the ITT population up to Week 24 was 38.9% in the FF/UMEC/VI group and 37.7% in the BUD/FOR group; the most common AEs were nasopharyngitis (7% and 5% for FF/UMEC/VI and BUD/FOR, respectively) and headache (5% and 6% for FF/UMEC/VI and BUD/FOR, respectively). A similar pattern was observed in the EXT population up to Week 52; the most common AEs were nasopharyngitis (11% and 10% for FF/UMEC/VI and BUD/FOR, respectively) and headache (8% and 10% for FF/UMEC/VI and BUD/FOR, respectively).

COPD worsening was one of the most common AEs in the BUD/FOR group (10%), but was less common in the FF/UMEC/VI group (2%) in the EXT population up to Week 52.

The incidence of major cardiovascular events was 0.4% and 0.8% in the ITT population up to Week 24, and 2.4% and 0.9% in the EXT population up to Week 52, for FF/UMEC/VI and BUD/FOR, respectively.

IMPACT Trial [2,10]

The most common adverse events (AEs) across treatment groups were viral upper respiratory tract infection, worsening of COPD, upper respiratory tract infection, pneumonia and headache. The incidences of the most frequent serious AEs were worsening of COPD (11%, 11% and 13% for FF/UMEC/VI, FF/VI and UMEC/VI, respectively); for pneumonia the incidences were 4%, 4% and 3% for FF/UMEC/VI, FF/VI and UMEC/VI, respectively.

Table of Adverse events for Trelegy ▼[3]

Incidence of Event	Adverse Event
Common (≥1/100 to <1/10)	Pneumonia, Upper Respiratory Tract Infection, Pharyngitis, Rhinitis, Influenza, Nasopharyngitis, Headache, Cough, Arthralgia, Back pain
Uncommon (≥1/1,000 to <1/100)	Candidiasis of mouth and throat, Viral Respiratory Tract Infection, Supraventricular tachyarrhythmia, Tachycardia, Atrial fibrillation, Oropharyngeal pain, Fractures
Not Known	Vision blurred

Strengths and limitations of the evidence:

Strengths:

- The studies were double blind, parallel group, randomised controlled trials with large patient numbers
- Results available for 52 weeks of treatment
- Allowed patients with COPD who also had significant cardiovascular disease to be enrolled.
- Patients remained on their current standard medications during the run -in period, in order to more reflect real life practice.

Limitations:

- Some exacerbations within the trials may have gone unreported
- Within the trials using medication count as a measure of adherence may be inaccurate
- 52 weeks may not be sufficient for assessing severe exacerbations requiring hospitalisation
- In FULFIL, the double dummy design was used to minimise the use of different dosage regimes i.e. once daily vs twice daily, but the full advantage/ disadvantage of the different dosage regimes may not have been demonstrated.

Prescribing and risk management issues:

This medicinal product is subject to additional monitoring under the MHRA black triangle scheme.

The licence for Trelegy 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 beta2-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 Trelegy to be used outside of its licence.

The current recommendation from the Global Initiative for Chronic Obstructive Lung Disease strategy document[6] (GOLD) for primary choice of a dual therapy; and their preferred route before 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.[6,11]

Commissioning considerations:

Anticipated patient numbers and net budget impact

Across the eight clinical commissioning groups of Lancashire and South Cumbria, 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%.[12] The proportion of COPD patients treated with triple therapy has been estimated to be between 23%[13] and 25.5%[14] equating to 8,855 - 9,819 patients across Lancashire and South Cumbria. However, one of the studies[13] 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 Trelegy this would incur an annual cost of £44.50 x 12 x 9000 = £4,806,000 and would allow for continuation within the Ellipta device pathway if an ICS/LABA/LAMA is required, using only one device and providing a cost saving versus the two Ellipta devices detailed in the current pathway.

The current 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

If 9,000 patients across Lancashire and South Cumbria were to be treated with Trimbow this would incur an annual cost of £44.50 x 12 x 9000 = £4,806,000 i.e. the same as with Trelegy

Associated additional costs or available discounts:

At a cost of £44.50 for 30 days treatment, Trelegy represents a cost saving compared with the open triple therapies currently recommended in the LMMG COPD pathway.

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:

Trelegy Ellipta will fit into the Ellipta device pathway in the LMMG COPD Guideline

Innovation, need, equity:

Trelegy provides for once daily dosing of a fixed triple therapy, in one inhaler device, which for the patients on the Ellipta pathway will offer continuation of the same device if and when escalation of therapy is warranted.

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 FULFIL Trial: Once-Daily Triple Therapy in Patients with Chronic Obstructive Pulmonary Disease. Lipson D A et al; Am J Respir Crit Care Med. 2017 Aug 15;196(4):438-446.

2 Data on File GSK December 2017

3 Summary of Product Characteristics Trelegy Ellipta 92 micrograms/55 micrograms/22 micrograms inhalation powder, pre-dispensed. https://www.medicines.org.uk/emc/medicine/34357 (accessed online 11th Deceber 2017)

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

5 Summary of Product Characteristics Trimbow 87 micrograms/5 micrograms/9 micrograms pressurised inhalation, solution. https://www.medicines.org.uk/emc/medicine/33828 (accessed online 11th December 2017)

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

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

8 http://www.lancashire.gov.uk/lancashire-insight/health-and-care/long-term-conditions/respiratory-disease.aspx (accessed online 11th December 2017)

9 Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: Results of two randomized studies. Siler T M et al; Respiratory Medicine 109 (2015) 1155-1163

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

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