BEDFORDSHIRE AND LUTON JOINT PRESCRIBING COMMITTEE (JPC)

18th September 2019
Revision date: September 2021

Bulletin 281: Fluticasone furoate/ umeclidinium/ vilanterol 92/55/22 micrograms inhalation powder (Trelegy® Ellipta®) for the treatment of COPD

JPC Recommendation:

- The committee agreed to add fluticasone furoate/ umeclidinium / vilanterol (Trelegy ® Ellipta® 92 microgram / 55 microgram / 22 microgram) to the formulary within it's licensed indication as a joint 1st-line triple therapy option (ICS / LAMA/ LABA) for the treatment of COPD.

Bedfordshire CCG
Luton CCG

New Medicine Review

Choice of combination Inhaled Corticosteroid (ICS, Long Acting Muscarinic Agent (LAMA) and Long Acting Beta Agonist (LABA) inhaler for Chronic Obstructive Pulmonary Disease (COPD)

Medicine	Fluticasone furoate/umeclidinium/ vilanterol 92/55/22 micrograms inhalation powder (Trelegy® Ellipta®)
Document status	Final, Approved September 2019
Date of last revision	August 2019
Proposed Sector of prescribing	Primary and secondary care
Introduction **Summary Key points** **Evidence level**	Fluticasone furoate/umeclidinium/ vilanterol 92/55/22 micrograms inhalation powder (Trelegy® Ellipta®) is a fixed dose combination inhaler containing an inhaled corticosteroid (ICS), a long-acting muscarinic antagonist (LAMA) and a long-acting beta agonist (LABA). There are currently 2 ICS/LABA/LAMA combination inhalers licensed for the maintenance treatment of patients with chronic obstructive pulmonary disease. Currently the formulary and COPD guidelines include beclomethasone/formoterol/glycopyrronium (Trimbow®). Clinical experience from Dr Bagmane at Bedford Hospital suggests once daily preparations are better at supporting patients that struggle to comply with twice daily.
The intervention **Mechanism of action**	Inhaled corticosteroid (ICS), long-acting muscarinic antagonist (LAMA) bronchodilator and long-acting beta agonist (LABA) bronchodilator. Trelegy® is provided in the Ellipta device which is also available to deliver LAMA (Incruse®), ICS/LABA (Relvar®) and LAMA/LABA (Anoro®) enabling device continuity for a patient throughout they COPD maintenance therapy.
Licensed indication	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 or a combination of a long-acting β2-agonist and a long-acting muscarinic antagonist

Formulation/Available Products	1. Trimbow® 87 micrograms/5 micrograms/9 micrograms pressurised inhalation, solution (beclomethasone/formoterol/ glycopyrronium)  2. Fluticasone furoate/umeclidinium/vilanterol (Trelegy® Ellipta) 92microgram/55microgram/22 micrograms, inhalation powder hard capsules. 
Usual dosage	One inhalation of Trelegy® Ellipta® 92/55/22 micrograms once daily.
Treatment alternatives/ place in therapy	The Bedfordshire and Luton COPD and ACO Guidelines recommend offering an ICS/LAMA/LABA if the patient experiences 2 or more exacerbations per year or severe exacerbations and a recent COPD hospital admission despite using a LAMA/LABA or LABA/ICS combination inhaler.
Future alternatives	
National guidance	NICE guidance (NG115) on Chronic Obstructive Pulmonary Disease recommends the use of ICS/LAMA/LABAs for the management of COPD in the following patients. For people with COPD who are taking LABA+ICS, offer LAMA+LABA+ICS if: • their day-to-day symptoms continue to adversely impact their quality of life or • they have a severe exacerbation (requiring hospitalisation) or • they have 2 moderate exacerbations within a year. For people with COPD who are taking LAMA+LABA, consider LAMA+LABA+ICS if: • they have a severe exacerbation (requiring hospitalisation) or • they have 2 moderate exacerbations within a year.

	For people with COPD who are taking LAMA+LABA and whose day-to-day symptoms adversely impact their quality of life:
	
	• consider a trial of LAMA+LABA+ICS, lasting for 3 months only
	• after 3 months, conduct a clinical review to establish whether or not LAMA+LABA+ICS has improved their symptoms:
	  ○ if symptoms have not improved, stop LAMA+LABA+ICS and switch back to LAMA+LABA
	  ○ if symptoms have improved, continue with LAMA+LABA+ICS.
	
	BTS GOLD guidelines (2019) recommend an ICS/LAMA/LABA for patients who develop further exacerbations despite using LABA/LAMA, an alternative option is to add roflumilast or azithromycin.
	
	Neither guidance makes a recommendation about which ICS/LAMA/LABA should be chosen but suggest that treatment should be individualised

Local Guidance	The Bedfordshire and Luton COPD and ACO Guidelines recommend offering an ICS/LAMA/LABA if the patient experiences 2 or more exacerbations per year or severe exacerbations and a recent COPD hospital admission despite using a LAMA/LABA or LABA/ICS combination inhaler. Trimbow (beclomethasone/formoterol/ glycopyrronium) is currently the only ICS/LAMA/LABA on the joint formulary for COPD.
Evidence for use	Taken from the NICE Evidence Summary (June 2018) In Lipson et al. 2018 (IMPACT), there was a statistically significant 15% reduction in the annual rate of moderate or severe exacerbations with fluticasone furoate/umeclidinium/vilanterol compared with fluticasone furoate/vilanterol (0.91 compared with 1.07 per year, rate ratio [RR] 0.85, 95% confidence interval [CI] 0.80 to 0.90; p<0.001). There was a 25% reduction compared with umeclidinium/vilanterol (0.91 compared with 1.21, RR 0.75, 95% CI 0.70 to 0.81; p<0.001, RCT, primary outcome, n=10,355, 52 weeks). In Lipson et al. 2018, there was no statistically significant difference between fluticasone furoate/umeclidinium/vilanterol and fluticasone furoate/vilanterol for the annual rate of severe exacerbations (0.13 compared with 0.15 per year, RR 0.87, 95% CI 0.76 to 1.01; p=0.06) and a statistically significant 34% reduction compared with umeclidinium/vilanterol (0.13 compared with 0.19 per year, RR 0.66, 95% CI 0.56 to 0.78; p<0.001). In Lipson et al. 2017 (FULFIL), there was a statistically significant improvement in the change from baseline in SGRQ total score with fluticasone furoate/umeclidinium/vilanterol compared with budesonide/formoterol after 24 weeks treatment (−2.2 units, 95% CI −3.5 to −1.0 units; p<0.001). However there was no statistically significant difference between the 2 groups after 52 weeks' treatment (−2.7 units, 95% CI −5.5 to 0.2 units; p=0.065, RCT, co-primary outcome, n=1,811 and n=430 for 52-week data). In Lipson et al. 2018, there were statistically significant improvements in the change from baseline in SGRQ total score with fluticasone furoate/umeclidinium/vilanterol compared with both fluticasone furoate/vilanterol (−1.8 units, 95% CI −2.4 to −1.1 units; p<0.001) and

	umeclidinium/vilanterol (−1.8 units, 95% CI −2.6 to −1.0 units; p<0.001; secondary outcome). However, the differences between the groups were less than the 4 units' decrease considered to be the minimum clinically important difference. In Lipson et al. 2017, there was a statistically significant improvement in the change from baseline in trough forced expiratory volume in 1 second (FEV1) with fluticasone furoate/umeclidinium/vilanterol compared with budesonide/formoterol (142 ml compared with −29 ml respectively; difference 171 ml, 95% CI 148 ml to 194 ml; p<0.001, co-primary outcome). In Lipson et al. 2018, more participants had a clinically significant improvement in TDI focal score with fluticasone furoate/umeclidinium/vilanterol compared with fluticasone furoate/vilanterol (36% compared with 29% respectively, odds ratio 1.36; 95% CI 1.19 to 1.55, p<0.001, RCT, additional outcome in a subset of participants, n=5,058, 52 weeks).
Safety*	Taken from the NICE Evidence Summary (June 2018) The European Public Assessment Report (EPAR) highlighted that pneumonia occurred more frequently in the fluticasone furoate/umeclidinium/vilanterol group than the budesonide/formoterol group in the Lipson et al. 2017 study (2.2% participants compared with 0.8% participants). The EPAR further added that the significance of this, if any, is uncertain as both groups contained an ICS and it is unknown if there are differences within the class for ICS propensity to cause pneumonia. The Medicines and Healthcare products Regulatory Agency issued a Drug Safety Update in October 2007 on the risk of pneumonia with inhaled corticosteroids. In Lipson et al. 2017 for the subset who continued treatment for 52 weeks the incidence of pneumonia was similar between the 2 groups (1.9% and 1.8%). There was no statistically significant difference between fluticasone furoate/umeclidinium/vilanterol and fluticasone furoate/vilanterol for the risk of pneumonia (hazard ratio [HR] 1.02, 95% CI 0.87 to 1.19; p=0.85). However, there was a statistically significant higher risk of pneumonia with fluticasone furoate/vilanterol/umeclidinium compared with umeclidinium/vilanterol (HR 1.53; 95% CI 1.22 to 1.92; p<0.001). According to the SPC the most commonly reported adverse reactions with fluticasone furoate/umeclidinium/vilanterol were nasopharyngitis (7%), headache (5%) and upper respiratory tract infection (2%).
Costs **Tariff status** **Activity costs**	

Drug & Dosage	**30 day cost/per patient**	**Annual Cost per patient**
Trelegy Ellipta® (Fluticasone furoate/umeclidinium/ vilanterol)	£44.50	£534
Trimbow (beclomethasone/formoterol/ glycopyrronium)	£44.50	£534

	N.B. Doses are for general comparison and do not imply therapeutic equivalence
Cost effectiveness (if available)	Taken from the NICE Evidence Summary (June 2018) The acquisition cost of fluticasone furoate/umeclidinium/vilanterol (Trelegy) is less than that of other combinations of ICS/LABA plus LAMA in 2 inhalers. A 30-day supply of treatment with fluticasone furoate, umeclidinium and vilanterol costs £44.50 (excluding VAT) when the triple-therapy inhaler (Trelegy) is prescribed. This compares with £49.50 (excluding VAT) when fluticasone furoate and vilanterol are prescribed in a dual-therapy inhaler (Relvar Ellipta, fluticasone furoate/vilanterol 92/22 micrograms) together with umeclidinium in a single-therapy inhaler (Incruse Ellipta).
Potential number of patients in Bedfordshire and Luton **Impact per 100,000 population** **Affordability considerations**	COPD prevalence is estimated at 2-4% but the diagnosed prevalence is about 1.5% (1,500 per 100,000) which increases to 10% in men aged over 75. (14) An average GP practice of 6,600 patients is likely to have about 100 patients on its COPD disease register. This equates to approximately 6,100 and 3,000 patients with COPD in Bedfordshire and Luton respectively.
Decisions from other bodies **Comments sought from –**	SMC and AWMSG have approved fluticasone/umeclidinium/vilanterol for maintenance treatment in patients with COPD. Milton Keynes Formulary has approved fluticasone furoate/umeclidinium/vilanterol for prescribing, Cambridgeshire and Peterborough formulary have it listed as non-formulary.
Evidence strengths and limitations	

PAC New Drug Template – Adapted from East Anglia Medicines Information, NHS Suffolk, NHS Cambridgeshire and NHS Derby templates

**Consult Summary of Prescribing Characteristics for full prescribing detail.*

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.

Appendix 1- Search Strategy

All Wales Medicines Strategy Group: COPD Management and Prescribing Guideline. May 2019. Accessed via www.awmsg.org

Trelegy Ellipta (fluticasone furoate 92 micrograms/umeclidinium 55micrograms/vilanterol 22micrograms) Summary of Product Characteristics. Accessed via www.medicines.org.uk on 28th August 2019.

BTS GOLD strategy for chronic obstructive pulmonary disease. December 2018, accessed via www.guidelines.org.uk

Drug Tariff, NHSBSA, August 2019 accessed via www.nhsbsa.nhs.uk

NICE Guidelines (NG115) Chronic obstructive pulmonary disease in over 16s: diagnosis and management. Updated July 2019, accessed via www.nice.org.uk

NICE Evidence Summary (ES18) Chronic obstructive pulmonary disease: fluticasone furoate, umeclidinium and vilanterol (Trelegy). June 2018, accessed via www.nice.org.uk

Trelegy Ellipta (fluticasone furoate 92 micrograms/umeclidinium 55micrograms/vilanterol 22micrograms) Summary of Product Characteristics. Accessed via www.medicines.org.uk on 28th August 2019.

Treatment assessed (Month and year): Choice of combination Inhaled Corticosteroid (ICS), Long Acting Muscarinic Agent (LAMA) and Long Acting Beta Agonist (LABA) inhaler for Chronic Obstructive Pulmonary Disease (COPD)
JPC Recommendation • The committee agreed to add fluticasone furoate/ umeclidinium / vilanterol (Trelegy ® Ellipta® 92 microgram / 55 microgram / 22 microgram) to the formulary within it's licensed indication as a joint 1st-line triple therapy option (ICS / LAMA/ LABA) for the treatment of COPD.
1) Clinical Effectiveness The evidence base shows that both ICS/LABA/LAMA inhalers are effective bronchodilators which produce clinically significant improvements in lung function (FEV1).
2) Cost Effectiveness Triple therapy with fluticasone furoate/umeclidinium/vilanterol (Trelegy) costs the same as triple therapy with beclometasone/formoterol/glycopyrronium (Trimbow) which is currently on the formulary.
3) Equity & Equality Impact Assessment* No impact envisioned
4) Needs of the community COPD prevalence locally is increasing and underdiagnosed.
5) Need for healthcare (incorporates patient choice and exceptional need) The choice of treatment for a person with COPD depends on drug efficacy, tolerability to treatment, possible adverse events and the suitability of different inhaler devices to the person. Inhaled long-acting bronchodilators have an important role to play in managing COPD.
6) Policy drivers NICE Clinical Guideline NG115 on COPD Bedfordshire and Luton COPD and ACO Guidelines
7) Disinvestment Potential for disinvestment in ICS/LABA/LAMA inhaler not recommended for use by the JPC.

The JPC agreed the following sections within the PCT Ethical and Commissioning Framework were not relevant to JPC discussions: Health Outcomes, Access, and Affordability.

***Equality Impact Assessment for BCCG only**

Where the implementation of the decision of the Bedfordshire and Luton Joint Prescribing Committee (JPC) may impact on one or more equality group differently to others, BCCG will require an equality impact assessment to be completed. The guidance on this can be found in the attached document. Please summarise the equality impact in the in the Equity & Equality Impact Assessment box above.

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Protected Characteristics (under the Equality Act):-

Age; Disability; Gender reassignment; Marriage & Civil Partnership (in employment only); Pregnancy & Maternity; Race; Religion & Belief; Sex; Sexual orientation; carers; other identified groups.

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*